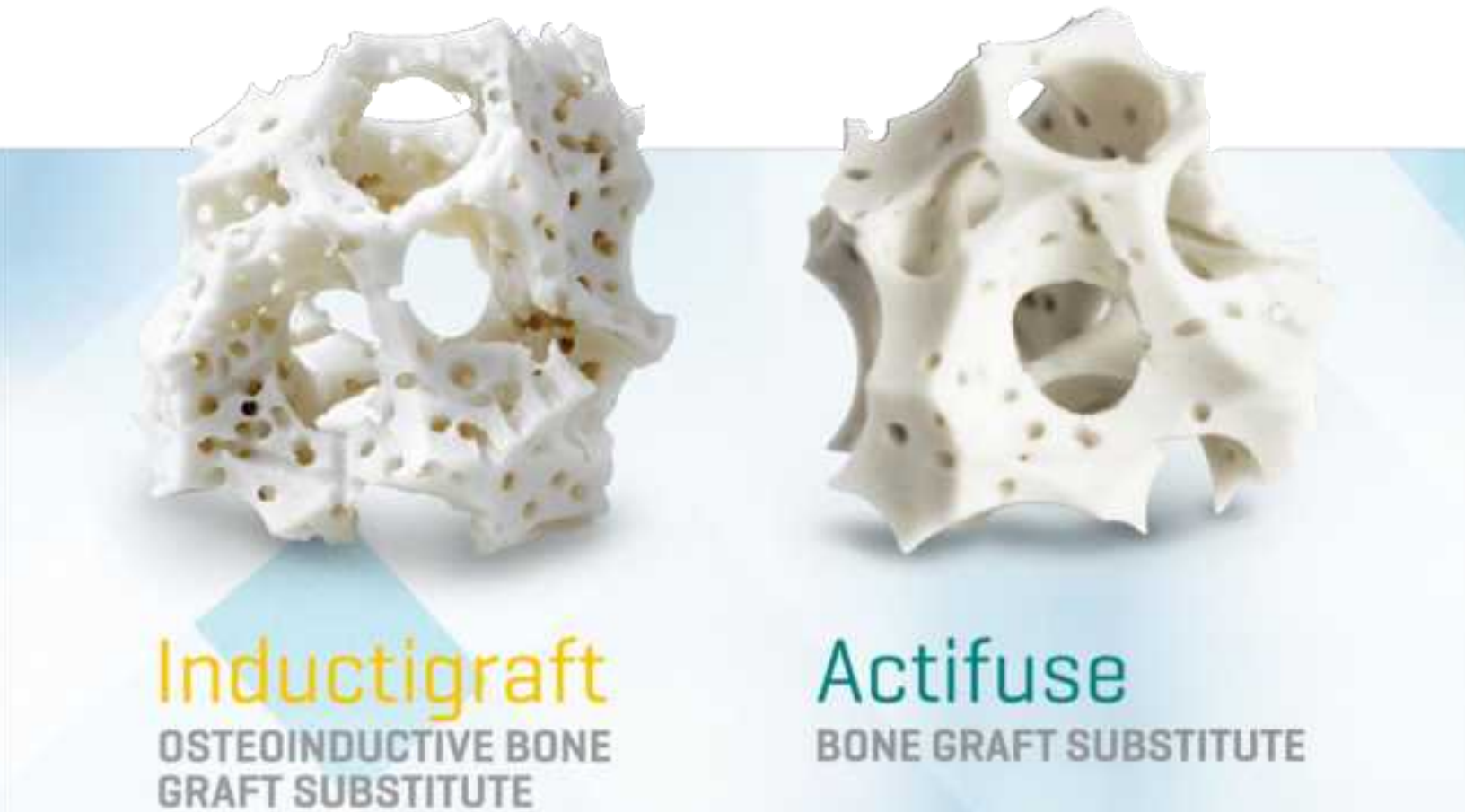
CLINICAL OVERVIEW

ORTHOBIOLOGIC CLINICAL PRIMER



GBU-AS2-210002 v1 3/2021

Baxter

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Use of a Fluorescent Probe to Monitor the Enhanced Affinity of rh-BMP-2 to silicated-calcium Phosphate Synthetic Bone Graft Substitutes under Competitive Conditions. Marc-Krystelle Mafina Alice C. Sullivan , Karin A. Hing Materials Science and Engineering- C80 (2017) pps. 207-212 s

INTRODUCTION

Within the biomaterials and orthobiologic industries, the competitive nature of protein adsorption has been of keen interest. Key to the performance of many biomedical devices, is the understanding or control of protein adsorption and structural confirmation in dependence of protein activity. This is relevant when considering synthetic bone graft substitutes (SBG). Further research needs to be done into approaches in tissue engineering that involves the seeding of porous biocompatible and/or biodegradable scaffolds. This study concentrates on understanding and monitoring the effect of protein adsorption into biocompatible and biodegradable scaffolds. The focus being on monitoring and understanding protein adsorption behavior observed from the scaffold in a competitive environment.

KEY HIGHLIGHTS

- A comparative investigation was undertaken on 1–2 mm sized granules of two forms of synthetic bone graft substitute (SBG) with identical pore structure but varied bulk chemistry, stoichiometric hydroxyapatite (HA) and silicate substituted (0.8 wt.% Si) hydroxyapatite (SA), to assess the influence of SBG chemistry on the relative affinity of an osteogenic growth factor (GF), recombinant human bone morphogenetic protein-2 (rhBMP-2). A previously described novel fluorescent probe, fluoresceinthioureidoaminocaproic acid (FTCA), was covalently attached to rhBMP-2 to give FTCA-rhBMP-2 and facilitate the quantitative monitoring of GF uptake and release from the two chemistries of SBG.
- The relative affinity of rhBMP-2 for the HA and SA granules was assessed at a physiologically relevant concentration of 300 ng mL^{-1} from three (increasingly complex) environments; phosphate buffered saline (PBS), minimum Eagles' medium (MEM) and serum supplemented MEM (SCEM) in order to closely mimic clinical bone repair procedures. The results demonstrated that rhBMP-2 affinity to SBGs was highly sensitive to both SBG chemistry and the composition of the local environment. Under the most physiologically relevant competitive conditions of SCEM, rhBMP-2 showed greater affinity to SA ($p < 0.05$) such that 50% of the rhBMP-2 in solution was adsorbed to the SA granules after only 15 min, as compared to 30% adsorbed to the HA granules.
- Subsequent investigation of the desorption of adsorbed GF from the SBGs demonstrated that a significantly higher percentage of the adsorbed rhBMP-2 was desorbed from HA as compared to SA granules. Together, these observations suggested that at physiologically relevant concentrations and conditions, rhBMP-2 has a greater affinity to silicate-substituted hydroxyapatite as compared to stoichiometric hydroxyapatite, which may in part explain the enhanced osteoconductive and reported osteoinductivity for silicate-substituted hydroxyapatite based SBGs.

Use of a Fluorescent Probe to Monitor the Enhanced Affinity of rh-BMP-2 to silicated-calcium Phosphate Synthetic Bone Graft Substitutes under Competitive Conditions. Marc-Krystelle Mafina Alice C. Sullivan , Karin A. Hing Materials Science and Engineering- C80 (2017) pps. 207-212 s

MATERIALS

All chemicals and reagents for the synthesis of the ceramic samples were obtained from VWR. Hydroxyapatite powders were produced via an aqueous precipitation route and porous granules were synthesized via a novel slip foaming technique. Recombinant human bone morphogenetic protein-2 (rhBMP-2) was purchased from Sera Laboratories (UK), phosphate buffer solution (PBS), minimum Eagles' medium (MEM), foetal bovine serum (FBS) and dialysis tubes were obtained from Sigma-Aldrich.

DISCUSSION

The aim of this study was to investigate the relative affinity of an osteogenic growth factor (GF), recombinant human bone morphogenetic protein-2 (rhBMP-2) for porous stoichiometric hydroxyapatite (HA) and silicate substituted hydroxyapatite (SA) synthetic bone graft (SBG) substitute granules from a series of increasingly complex environments. Our objective was to confirm or refute our hypothesis that one mechanism of action by which SA SBG may enhance new bone formation in vivo is via modification of the osteogenic response through the enrichment of key adhesion proteins and growth factors that combine to recruit both pre-committed osteogenic and stem cells and direct their differentiation down an osteogenic pathway.

RESULTS

- No plateau of FTCA-rhBMP-2 adsorption was observed on SA or HA SBG in PBS, suggesting that the medium's chemistry and interactions with BMP-2 did not have a pronounced effect on the mechanisms of the growth factor's adsorption as compared to the SBG's chemistry. Differences observed between the tests were defined by the maximal amounts adsorbed, found to be higher on the silicate bone graft substitute as compared to the stoichiometric bone graft.
- The patterns observed in MEM as compared to PBS for both SBG clearly suggest an influence of this medium's more complex chemistry on the affinity of the growth factor, as maximal adsorption occurred within the first minute and plateaued throughout the remainder of the experiment with no significant difference between the maximal adsorbed amounts on HA or SA SBGs. In this environment, FTCA-BMP-2 adsorption appeared to be more sensitive to medium interactions, irrespective of the chemistry of the SA or HA SBG
- In summary, this study clearly showed not only the importance of the scaffolds surface chemistry on the affinity of FTCA-rhBMP-2 to bone graft substitute scaffold materials, but also the influence of the chemistry of the local physiological environment on its adsorption behavior. The BMP adsorption behaviors with the biomaterials in the different mediums are different. For HA granules, additional protein inhibited the BMP binding; but for SA granules, additional protein did not affect the final adsorption quantity. It also demonstrated that, by

using a physiologically relevant concentration of rhBMP-2 labelled with a novel fluorescent probe, silicate substituted hydroxyapatite has a greater affinity for rh-BMP-2 than stoichiometric hydroxyapatite under competitive conditions. This finding supports our hypothesis that there may be a chemotactic dependence behind the enhanced osteoconductive observed for specific bulk chemistries of bone graft substitute material, relating to these grafts possessing surface physio-chemistries that sequester and enrich key adhesion proteins, angiogenic and osteogenic growth factors to confer apparent osteoinductivity behavior on the synthetic scaffolds.

CONCLUSIONS

- The binding affinity of rhBMP-2 for porous silicate substituted and a stoichiometric hydroxyapatite synthetic bone graft granule was investigated in a series of increasingly complex environments. Both the composition of the local physiological environment and the chemistry of the synthetic bone graft granules were found to impact on rhBMP-2 adsorption and desorption. Under the most physiologically relevant competitive conditions of 10% serum supplemented minimum Eagles medium, silicate substituted hydroxyapatite was found to possess a greater affinity for rhBMP-2 than stoichiometric hydroxyapatite.
- These observations support the hypothesis that the enhanced bioactivity of these grafts' materials may in part be related to their ability to sequester and enrich key adhesion proteins, angiogenic and osteogenic growth factors to confer apparent osteoinductivity behavior on the synthetic scaffolds.

Assessment of Si-CaP 30 in a Rabbit Posterolateral Fusion Model with Concurrent Chemotherapy (Abstract) Joseph D. Smucker, Emily B. Petersen, Ali Al-Hili, James V. Nepola, Douglas C. Fredericks The Iowa Orthopaedic Journal, ABSTRACT, Vol. 33, pps. 140-146

INTRODUCTION

A randomized, controlled study in a laboratory setting with blinded assessment of fusion by manual palpation and flexibility testing. Sixty rabbits were studies with 45 used for analysis. A modified chemotherapy protocol described by Morcuende, which utilized multiple treatments of cisplatin and doxorubicin to slow the bone formation rate associated with healing grafts. It was then hypothesized that a bone graft substitute with modified chemical and structural properties could increase bone formation in this challenging environment.

The objective of this study was to determine the performance characteristics of Si-CaP 30 (INDUCTIGRAFT) as a bone graft substitute compared to autograft (iliac crest bone graft [ICBG], ACTIFUSE ABX and β-Tricalcium Phosphate-Bioactive Glass-Type I Collagen (βTCP-BG) in a rabbit posterolateral spine fusion model with concurrent chemotherapy treatment. In this investigation, two silicon-based HA formulations (INDUCTIGRAFT and ACTIFUSE ABX) and a βTCP—bone graft material (Vitoss BA) were evaluated in a posterolateral spine fusion model with concurrent administration of chemotactic drugs.

METHODS

During this study, 60 male skeletally mature New Zealand White rabbits weighing 4.5-5.5 kg were used. The number of rabbits in total and per group was determined by a power analysis to show a 20% difference in flexion/extension via biomechanical testing (alpha of 0.05 and a power of 90). The rabbits were individually caged and monitored daily for signs of pain and discomfort.

The rabbits received cisplatin and doxorubicin intravenously (2.5 mg/kg) 7 days before surgery and again at 7, 14 and 21 days after surgery. Complete blood panels and chemistries were used to assess the health status of the rabbits during the study.

Surgical Procedure

All surgical procedures were performed in a surgical suite using inhalation anesthesia and aseptic techniques. Rabbits were placed flat on the operating table and surgically prepped with 70% povidone-iodine solution. A single level posterolateral intertransverse process fusion was performed in 58 rabbits. The rabbits in the autograft group were given approximately 2.5-3.0 cc of corticocancellous bone graft obtained bilaterally from the iliac crest. This volume of graft is the maximum amount which can be harvested from the rabbit iliac crest without significant animal morbidity. The implant materials were administered as stand-alone grafts that were not mixed with autologous bone nor autologous bone marrow aspirate. Approximately 3.0 cc of implant material was placed bilaterally.

Manual Palpation Analysis

Primary assessment used to determine fusion was manual palpation and flexibility analysis. After removing the spine, fusion was graded by three independent blinded observers as "fused" if no detectable motion was present at the treated segment when tested in flexion and extension. The fusion was graded as 'not fused' if motion was present. Final results were determined by agreement of at least two of the three observers.

Mechanical Testing

Flexibility assessments of lumbar motion and stiffness involved biomechanical, non-destructive load testing. Stiffness was verified and compared with normal controls (10 normal rabbit lumbar columns), historic controls and literature. Motion segments were considered fused if motion was less than 5.5° in flexion/extension.

Radiographic Assessment

All rabbits were radiographed at 0, 4, 6, 8- and 12-weeks post-surgery. Peripheral quantitative computer tomography analysis of all specimens was performed at 0 and 12 weeks (study end) to demonstrate quantitative change in bone mineral density over time.

Histology

Four rabbits from each group were randomly selected for histological evaluation. New bone formation/bone maturation was scored on a scale of 0-4 where a score of 0 represented has less that 25% lamellar bone and a score of 4 greater than 75% lamellar bone in the paraspinal bed. Residual implant was also scored on a scale of 0-4 with 0 representing no remaining implant present and 4 having greater than 50% of the fusion mass containing residual graft. Fusion was scored using a scale of 1-10 where a score of 10 represented complete bridging of the TPs with mature bone.

RESULTS

Fifteen rabbits were omitted from the study due to surgical and chemotherapy treatment complications. The remaining 45 rabbits included in the study were evaluated by manual palpation, flexibility and histological criteria.

Assessment of Si-CaP 30 in a Rabbit Posterolateral Fusion Model with Concurrent Chemotherapy (Abstract) Joseph D. Smucker, Emily B. Petersen, Ali Al-Hili, James V. Nepola, Douglas C. Fredericks The Iowa Orthopaedic Journal, ABSTRACT, Vol. 33, pps. 140-146

Manual Palpation Assessment of Fusion

At 12 weeks post-surgery:

- Manual palpation of the treated motion segment demonstrated successful fusion in 45% (5/11) of the autograft group
- 33% (4/12) in the ACTIFUSE ABX group
- 0% (0/11) in the Vitoss BA group
- INDUCTIGRAFT group demonstrated successful fusion in 82% (9/11; Table 1)

Table 1. Manual palpation results at week 12 post surgery

	ICBG	Vitoss BA	ACTIFUSE ABX	SiCaP-30
Pseudoarthrosis % (n/N)	54.5 (6/11)	100 (11/11)	67 (8/12)	18 (2/11)
Fusion rate % (n/N)	45 (5/11)	0 (0/11)[a]	33 (4/12)[b]	82 (9/11)[a,b]

ICBG= iliac crest bone graft; Superscript letters denote statistical differences between pairs with Fishers exact tests; [a] = P=0.002; [b] = 0.0361

Mechanical Testing of Motion and Fusion

Flexion-extension values were used to measure the motion of the lumbar spine. The INDUCTIGRAFT group had a reduced range of motion compared with the other treatment groups; this difference achieved statistical significance (Figure 1)

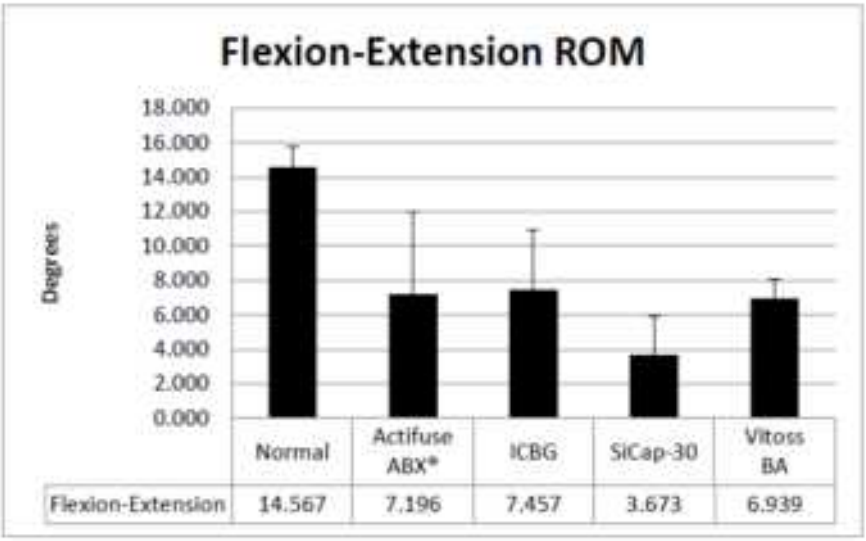

Figure 1. Flexion-extension range of motion (ROM). Lumbar motion was measured 12 weeks post surgery in normal untreated/ unfused rabbit spines, Actifuse ABX, iliac crest bone graft (ICBG), SiCaP-30 and Vitoss BA treated groups. *SiCaP-30 had significantly less motion when compared to all other groups tested ($p<0.05$).

Assessment of Si-CaP 30 in a Rabbit Posterolateral Fusion Model with Concurrent Chemotherapy (Abstract) Joseph D. Smucker, Emily B. Petersen, Ali Al-Hili, James V. Nepola, Douglas C. Fredericks The Iowa Orthopaedic Journal, ABSTRACT, Vol. 33, pps. 140-146

Individual rabbits in all treatment groups were compared with normal motion was of the lumbar spine, determined by measuring the flexibility of 10 unfused/untreated rabbit lumbar spinal columns. Range of motion scores determined by manual palpation (Table 2):

- Flexibility testing demonstrated fusion success in 36% (4/11) of the autograft group
- 25% of the ACTIFUSE ABX group
- 0% (0/11) in the Vitoss BA group
- 82% (9/11) of the INDUCTIGRAFT group

Table 2. Physiologic range of motion of normal, pseudarthrosis and fused spine

Flexion/Extension	ICBG	Vitoss BA	ACTIFUSE ABX	SiCaP-30
ROM*				
Normal	14.567 (± 1.19)	14.567 (± 1.19)	14.567 (± 1.19)	14.567 (± 1.19)
Pseudarthrosis	9.906 (± 2.13)	6.939 (± 1.15)	9.391 (± 4.05)	7.58 (± 0.80)
Fused	4.518 (± 2.12)	n/a	4.122 (± 2.63)	2.805 (± 1.21)
Fusion rate % (n/N)*	36 (4/11)	0 (0/11)*	25 (3/12)	82 (9/11)*

ICBG= iliac crest bone graft; ROM = range of motion; *Fusion was defined as less than 5.5 on flexion-extension testing; Superscript letters denote statistical differences between pairs with Fishers exact tests; * = P<0.002

Radiology

Bone mineral density of the fusion masses was analyzed. The INDUCTIGRAFT and autograft group had the greatest bone mineral density increase from the day after surgery to time of euthanasia (+29% and +26%) followed by Vitoss BA (+18%) and ACTIFUSE ABX (14%). Figure 2

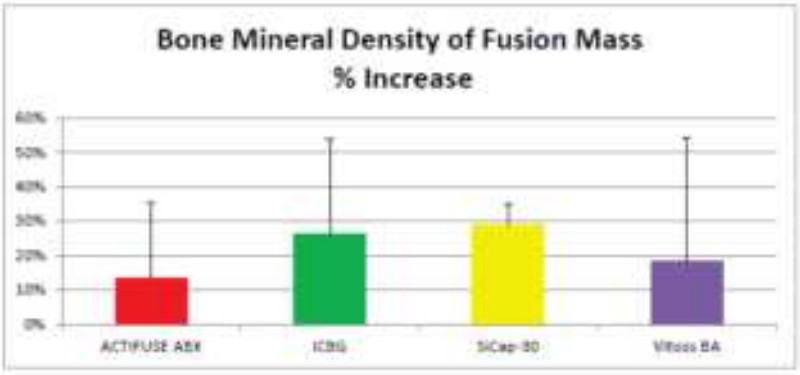

Figure 2. Bone mineral density of the fusion mass. SiCaP-30 demonstrated the greatest change in bone density, followed by iliac crest bone graft, Vitoss BA and Actifuse ABX.

Assessment of Si-CaP 30 in a Rabbit Posterolateral Fusion Model with Concurrent Chemotherapy (Abstract) Joseph D. Smucker, Emily B. Petersen, Ali Al-Hili, James V. Nepola, Douglas C. Fredericks The Iowa Orthopaedic Journal, ABSTRACT, Vol. 33, pps. 140-146

Histology

Blinded histological assessments were made on each histological specimen by a board-certified veterinary pathologist. There were no inflammatory reactions at the grafted sites regardless of implant. (Table 3 and Figure 3)

Table 3. Histological assessment* of new bone formation, fusion, and residual implant

	Fusion Score		New bone formation/Bone Maturation		Residual Implant	
	Pseudarthrosis	Fused	Pseudarthrosis	Fused	Pseudarthrosis	Fused
ICBG	5.00 (n=2)	5.25 (n=2)	2.00 (n=2)	2.00 (n=2)	2.00 (n=2)	2.00 (n=2)
Vitoss BA	1.00 (n=4)	n/a	1.00 (n=4)	n/a	2.78 (n=4)	n/a
ACTIFUSE ABX	3.50 (n=2)	4.75 (n=2)	1.00 (n=2)	1.00 (n=2)	3.00 (n=2)	3.00 (n=2)
SiCaP-30	4.50 (n=2)	5.00 (n=2)	1.00 (n=2)	1.00 (n=2)	3.00 (n=2)	3.00 (n=2)

*Fusion was scored using a 1–10 scale where a score of 10 was complete bridging of the TPs with mature bone. NBF was scored on a 0–4 scale. Residual implant was based on a range of 0–4 with a score of 4 having >50% of the implant present.

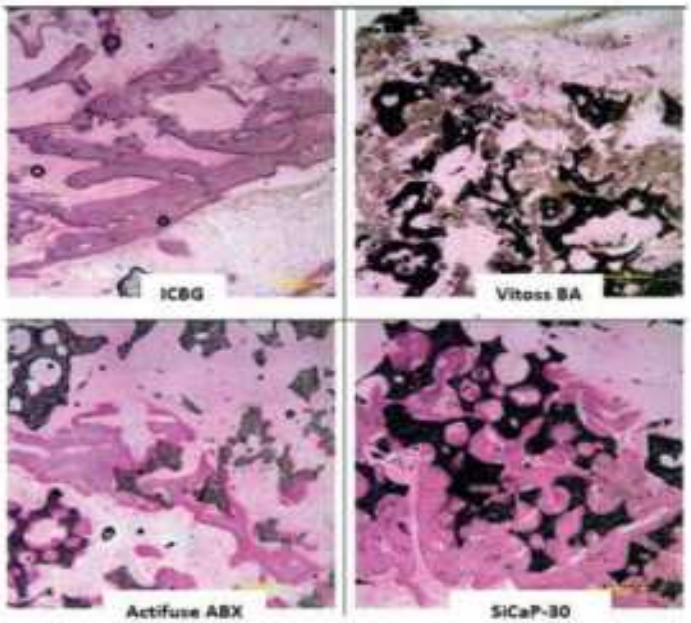

Figure 3. New bone formation. Microphotographs demonstrating new bone formation in the Actifuse ABX, SiCap-30 and ICBG treated groups. No new bone formation was evident in the Vitoss BA group. Both the Actifuse ABX and SiCaP-30 groups had new bone formation in direct apposition to the ceramic granules and connecting individual granules to adjacent granules.

Assessment of Si-CaP 30 in a Rabbit Posterolateral Fusion Model with Concurrent Chemotherapy (Abstract) Joseph D. Smucker, Emily B. Petersen, Ali Al-Hili, James V. Nepola, Douglas C. Fredericks The Iowa Orthopaedic Journal, ABSTRACT, Vol. 33, pps. 140-146

CONCLUSIONS

Rabbit model used in this study established that autograft had a reduced healing rate in contrast with published historical rates. The highest fusion rates were observed with INDUCTIGRAFT which also correlated with the lowest lumbar motion. ACTIFUSE ABX and ICBG had similar healing rates and Vitoss BA had little evidence of healing. The outcomes highlight the efficacy of the chemotherapy model for examining the performance characteristics of bone graft substitutes and overall rates of healing. Further studying in higher order animal species are required, however, modified silicate-substituted graft materials in the form of macro and microporosity may have significant bearing on their healing characteristics in challenging fusion models.

INTRODUCTION

The effectiveness of Si-CaP EP (INDUCTIGRAFT) as a separate graft is well-established. Examining the efficacy of combining INDUCTIGRAFT with autograft (ICBG) and bone marrow aspirate (BMA) in an extremities model has not been investigated. INDUCTIGRAFT was evaluated in an ovine distal femoral critical sized metaphysical defect as a standalone bone graft; as an ICBG extender (INDUCTIGRAFT/ICBG); and when mixed with bone marrow aspirate (INDUCTIGRAFT/BMA). Deficiencies were assessed after 4, 8 and 12 weeks with radiography, decalcified paraffin-imbedded histopathology, non-decalcified resin-embedded histomorphometry and mechanical indentation testing.

In this study, INDUCTIGRAFT was evaluated as a standalone bone graft, mixed with BMA, and mixed with ICBG in a sheep distal femoral critical sized defect model.

MATERIALS AND METHODS

Implants

- Si-CaP EP was evaluated as a standalone mixed with BMA obtained from the sternum in a 2:1 ratio (INDUCTIGRAFT/BMA) or INDUCTIGRAFT mixed with autologous ICBG in a 1:3 ration (INDUCTIGRAFT/ICBG). These configurations were selected to demonstrate that:
- INDUCTIGRAFT is efficacious as a standalone bone graft
- INDUCTIGRAFT is efficacious when mixed with BMA up to a ratio of 2:1 (and any mixture ratio in between 100% INDUCTIGRAFT and INDUCTIGRAFT/BMA in a 2:1 ratio)

Surgical Procedure

Adult female sheep (≥12 months) underwent bilateral surgery on the distal femur with two defects (approximately 8 mm diameter with 15 mm depth) created on the medial side of each femoral condyle (four defects per animal).

Bone healing was assessed after three time points: 4 weeks (W4), 8 weeks (W8), and 12 weeks (W12) of implantation.

Statistical Analysis

SigmaS-tat software was used for the statistical testing and measurements of possible differences between the histomorphometric, histopathologic and mechanical groups. INDUCTIGRAFT was compared to INDUCTIGRAFT/BMA and INDUCTIGRAFT/ICBG in separate evaluations of each time point. Equal variance and normality tests were completed. When both were effective, one-way analysis of variance (ANOVA) was used (with Tukey's post hoc tests for the appropriate multiple comparisons). When either equal variance or normality tests were unsuccessful, a Kruskal-Wallis analysis was used to

establish if statistical substance existed and pairwise impact was determined with Wilcoxon's Mann-Whitney *U* test. Differences were considered statistically significant when $P \leq 0.05$.

RESULTS

Early Death and Implantations

Three of the implanted animals did not survive until scheduled euthanasia, however, the cause of death was not related to the implantation of the Test Articles.

Table 1: Implantations Overview

	# of Defects	W4 Cohort	W8 Cohort	W12 Cohort	Histopathology/ Histomorphometry	Mechanical Testing
N = 5	30	X			X	X
N = 6	36		X		X	X
N = 7	42			X	X	X
N = 12 (Control Group)						X

High-resolution Radiography

No evidence of fracture between defects could be observed after evaluation of the radiographs at all time points. Macroscopic analysis of the implantation sites equally demonstrated no apparent fracture between the implant sites at all time points.

Efficacy of Silicate-Substituted Calcium Phosphate with Enhanced Strut Porosity as a Standalone Bone Graft Substitute and Autograft Extender in an Ovine Distal Femoral Critical Defect Model Stacy A. Hutchens, Charlie Campion, Michel Assad, Madeleine Chagnon, Karin A. Hing J Mater Sci: Mater Med (2016), New York 27:20

Mechanical Testing

The compressive modulus of elasticity of INDUCTIGRAFT/ICBG-treated defects were equivalent to that of the Controls after 4 weeks of implantation. (Fig. 1)

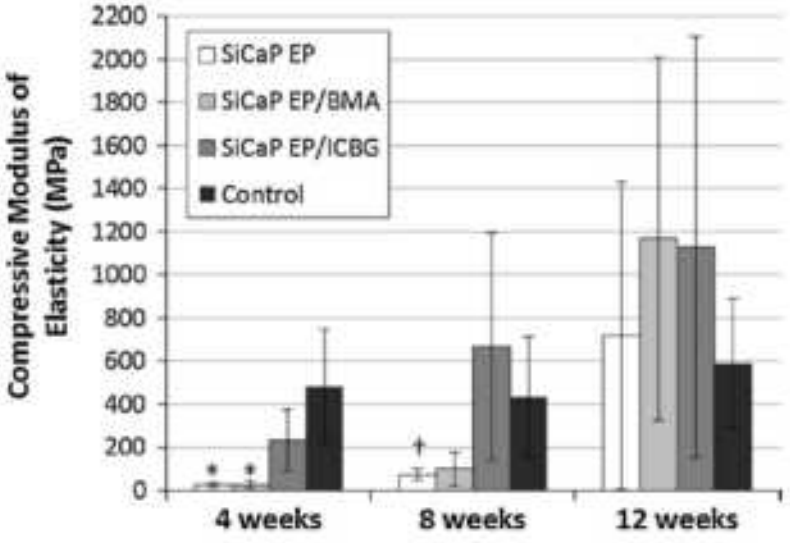

Fig. 1 Defects treated with silicate-substituted calcium phosphate with enhanced porosity mixed with iliac crest bone graft (SiCaP EP/ICBG) had a greater compressive modulus of elasticity at early time points when compared to treatment with stand-alone (SiCaP EP) or mixed with bone marrow aspirate (SiCaP EP/BMA), but all three groups had comparable properties at 12 weeks. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: *asterisk* significant difference versus Control ($P < 0.05$), *dagger* significant difference versus SiCaP EP/ICBG ($P < 0.05$)

Efficacy of Silicate-Substituted Calcium Phosphate with Enhanced Strut Porosity as a Standalone Bone Graft Substitute and Autograft Extender in an Ovine Distal Femoral Critical Defect Model Stacy A. Hutchens, Charlie Campion, Michel Assad, Madeleine Chagnon, Karin A. Hing J Mater Sci: Mater Med (2016), New York 27:20

After 8 weeks post-op, the stiffness of all treated defects was statistically equivalent to that of the Controls, with the stiffness of INDUCTIGRAFT/ICBG treated defect being significantly greater than those treated with INDUCTIGRAFT. There was no significant difference in compressive modulus of elasticity between any of the treated defects or the controls. Similar patterns of behavior were seen for the compressive yield strength. (Figure 2)

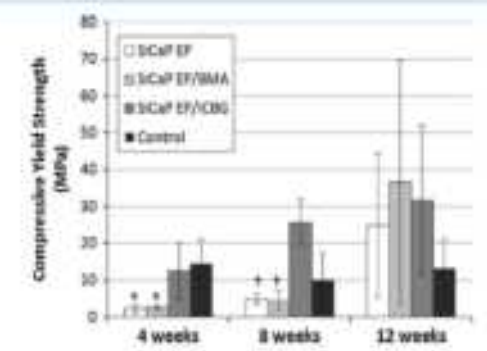

Fig. 2 Defects treated with silicate-substituted calcium phosphate with enhanced porosity mixed with iliac crest bone graft (SiCaP EP/ICBG) had a higher compressive yield strength at early time points compared to treatment with stand-alone (SiCaP EP) or mixed with bone marrow aspirate (SiCaP EP/BMA), but all three groups had comparable properties at 12 weeks. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: asterisk significant difference versus Control ($P < 0.05$), dagger significant difference versus SiCaP EP/ICBG ($P < 0.05$)

Similar patterns of behavior were seen for the ultimate compressive strength, with the exception at 8 weeks, strength values for INDUCTIGRAFT/ICBG-treated defects were significantly greater that those treated with INDUCTIGRAFT and INDUCTIGRAFT/BMA. (Figure 3)

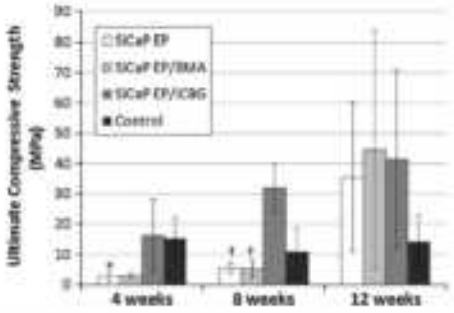

Fig. 3 Defects treated with silicate-substituted calcium phosphate with enhanced porosity mixed with iliac crest bone graft (SiCaP EP/ICBG) had a higher ultimate compressive strength at early time points when compared to treatment with stand-alone (SiCaP EP) or mixed with bone marrow aspirate (SiCaP EP/BMA), but all three groups had comparable properties at 12 weeks. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: asterisk significant difference versus Control ($P < 0.05$), dagger significant difference versus SiCaP EP/ICBG ($P < 0.05$)

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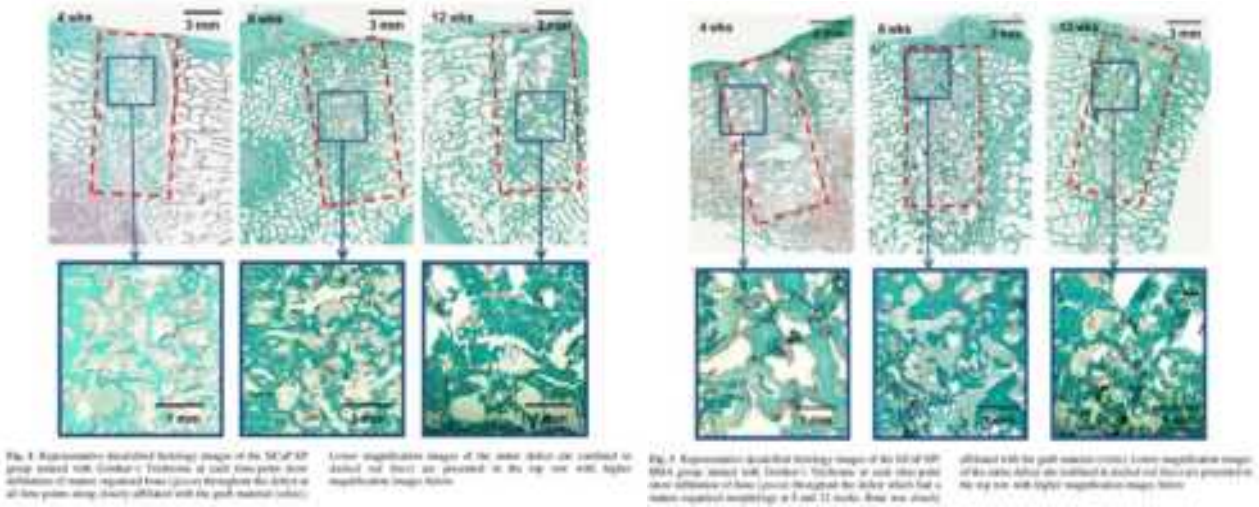
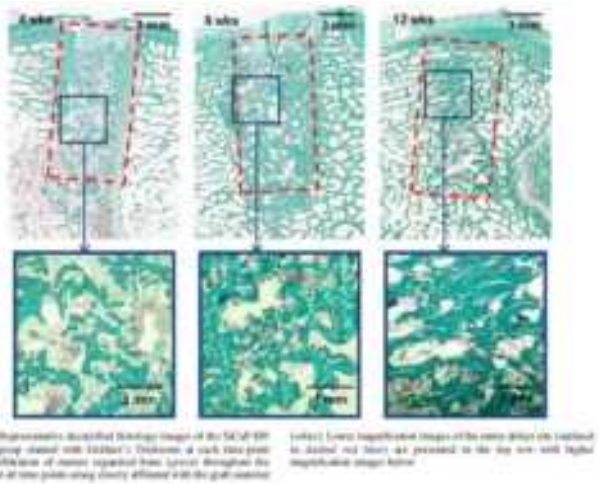
Decalcified Histopathology

At 4 weeks:

- Bone formed in the INDUCTIGRAFT (Fig. 4) and INDUCTIGRAFT/ICBG (Fig. 5) treated defects appeared more mature and organized than the bone in the INDUCTIGRAFT/BMA (Fig. 6).
- Bone morphology appeared comparable at 8 and 12 weeks amongst all three test groups
- Necrosis, infection, fibrinous exudates and tissue degeneration were not seen on any of the implant sites at all time points.
- Fatty infiltrate was not observed in any implant sites at 4 weeks.
- At 8 and 12-weeks post-implantation, polymorphonuclear cell infiltration and plasma cell infiltration were not seen in any implant sites.





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Residual graft material was contained in all defect sites distributed as multifocal granules or sometimes aggregates that served as nodes for new bone formation or were being incorporated or totally surrounded by new bone. Based on the absence of adverse tissue effects and the mild tissue reaction to the implant materials, healing of the implant sites appeared to be progressing in a normal fashion at all time points.

Non-decalcified Histomorphometry

No statistical difference in absolute Bone Volume (BV) percentages were found between the different treatment groups at 8 and 12-weeks, even though the mean absolute BV percentage was significantly higher in the INDUCTIGRAFT/ICBG group when compared to the INDUCTIGRAFT and INDUCTIGRAFT/BMA group at 4 weeks. (Fig. 7)

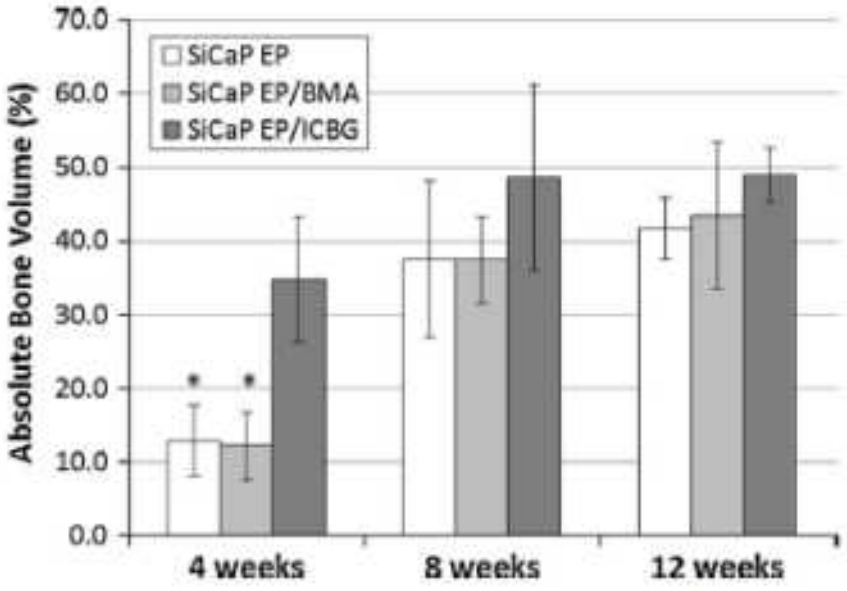

Fig. 7 The SiCaP EP/ICBG group had a higher absolute bone volume percentage at 4 weeks when compared to treatment with stand-alone (SiCaP EP) or mixed with bone marrow aspirate (SiCaP EP/BMA) but all three groups had comparable properties at 8 and 12 weeks. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: *asterisk* significant difference versus SiCaP EP/ICBG ($P < 0.05$)

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The INDUCTIGRAFT/ICGB group had higher normalized BV compared to the INDUCTIGRAFT/BMA group at 4 weeks, but no substantial differences were observed at 8 and 12-weeks. (Fig. 8)

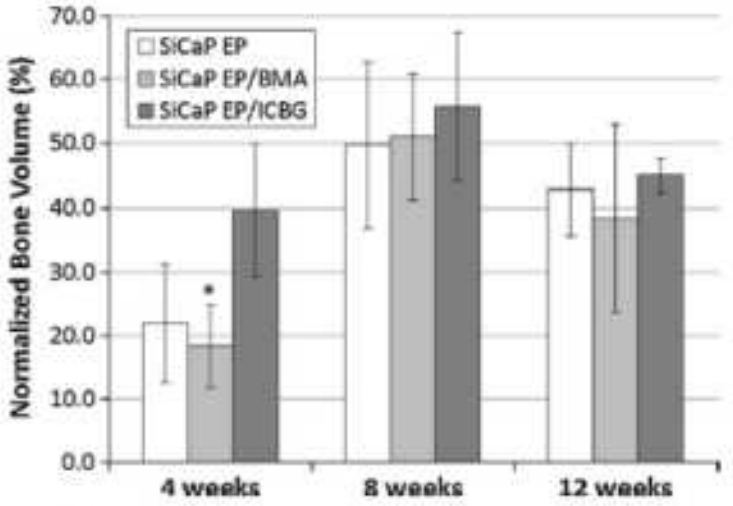

Fig. 8 The SiCaP EP/ICBG group had equivalent normalized bone volume percentage compared to treatment with stand-alone (SiCaP EP) at all time points. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: *asterisk* significant difference versus SiCaP EP/ICBG ($P < 0.05$)

At 4, 8 and 12-weeks, the mean absolute Graft Volume (GV) percentage was significantly lower in the INDUCTIGRAFT/ICBG group when compared to the INDUCTIGRAFT AND INDUCTIGRAFT/BMA groups. (Fig. 10)

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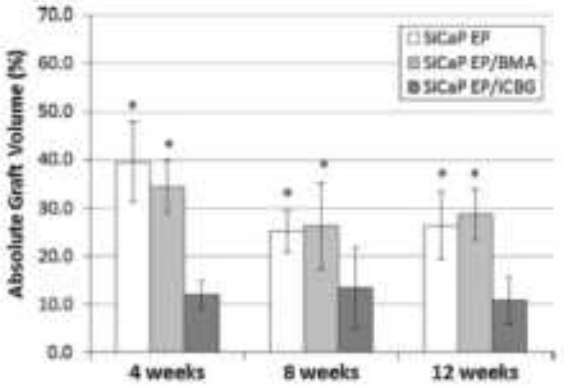

Fig. 9 The SiCaP EP and SiCaP EP/BMA groups had more absolute graft volume percentage compared to the extender group (SiCaP EP/ICBG). Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: asterisk significant difference versus SiCaP EP/ICBG ($P < 0.05$)

Mean absolute BV percentage in the defects increased over time in all three groups, with significantly higher mean absolute BV percentages at week 8 and week 12 when compared to week 4.

Mean absolute GV percentages significantly decreased at week 8 in the INDUCTIGRAFT groups compared to week 4 (indicating graft resorption), while GV percentages were statistically similar at weeks 8 and 12 (Fig.10)

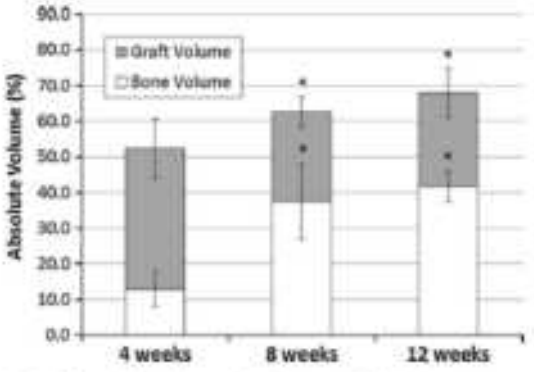

Fig. 10 The absolute bone volume increased (indicating osteoconduction) and absolute graft volume decreased (indicating graft resorption) over time in defects treated with SiCaP EP. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: *$P < 0.05$ compared to 4 weeks

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The drop in absolute GV from 4 to 8 and/or 12 weeks was not statistically significant per this pattern of behavior followed by INDUCTIGRAFT/BMA treated defects. (Fig. 11)

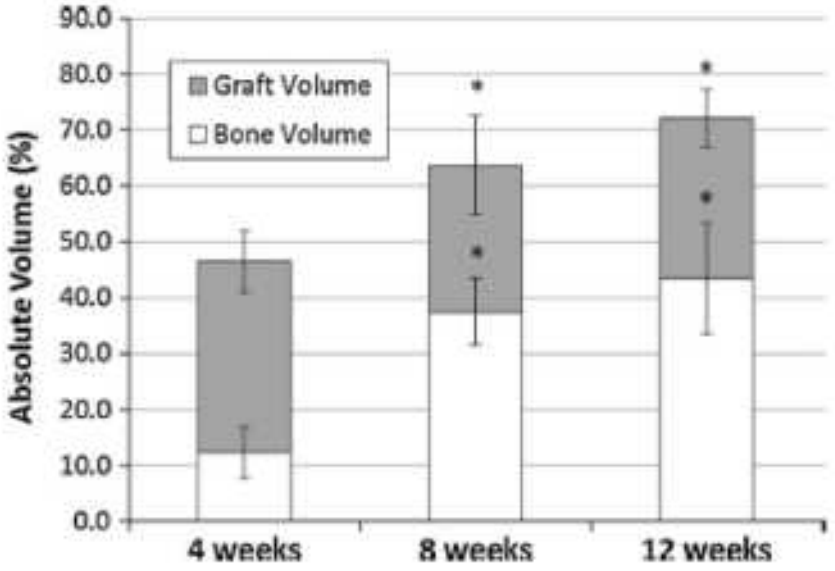

Fig. 11 The absolute bone volume increased over time (indicating osteoconduction) in defects treated with SiCaP EP/BMA. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: $^{*}P < 0.05$ compared to 4 weeks

There was relatively little variation in INDUCTIGRAFT/ICBG over the entire period of the study in contrast to the other 2 groups. (Fig. 12)

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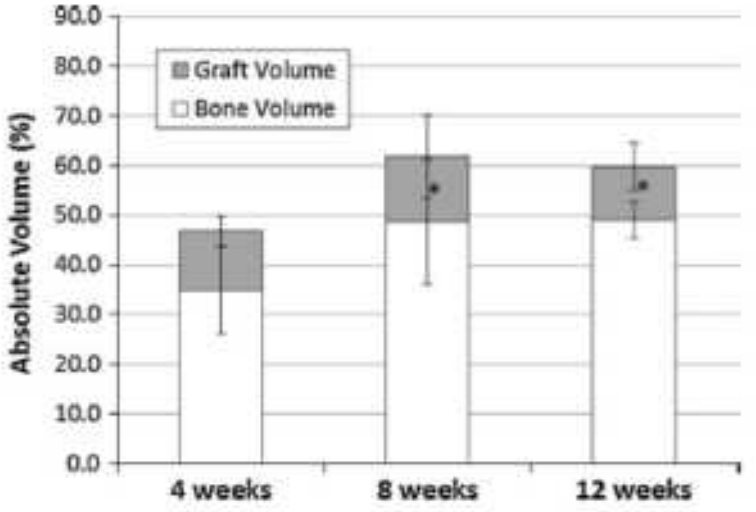

Fig. 12 The absolute bone volume increased over time (indicating osteoconduction) in defects treated with SiCaP EP/ICBG. Data was statistically assessed with one-way ANOVA and Tukey's post hoc test for normal/equal variance data and Kruskal–Wallis analysis with Wilcoxon's Mann–Whitney *U* test for data that did not pass normality/equal variance tests: $^{*}P < 0.05$ compared to 4 weeks

CONCLUSIONS

The data from this study confirmed that all materials exhibited excellent safety and biocompatibility as evidenced by a mild post-operative tissue reaction. However, INDUCTIGRAFT/ICBG appeared more favorable mechanical properties and produced more absolute BV percentage compared to INDUCTIGRAFT and INDUCTIGRAFT/BMA at early time points, though all three groups had comparable properties at 12 weeks.

Therefore, this study validates that INDUCTIGRAFT is powerful as a standalone bone graft substitute, mixed with BMA and as an ICBG extender.

Silicate-substituted Calcium Phosphate with Enhanced Strut Porosity Stimulates Osteogenic Differentiation of Human Mesenchymal Stem Cells Roberta Ferro De Godoy • Gordon Blunn Journal of Materials Science: Materials in Medicine Publisher: Springer US (NY) (2015): pps:1-12. C.Campion • S. Hutchens Baxter Healthcare Corporation, 1 Baxter Bkwy, Deerfied IL 60015 Email: stacy_hutchens@baxter.com This study was funded by Baxter Healthcare

INTRODUCTION

Many synthetic ceramic bone graft substitutes (BGSs) have osteoconductive properties (e.g. provide a physical scaffold for osteointegration of surrounding bone tissue), certain BGSs are osteostimulative meaning that they actively upregulate mesenchymal stem cell proliferation and stimulate differentiation into osteoblast-like cells.

The osteostimulative properties of silicate-substituted calcium phosphate with enhanced porosity (Si-CaP EP), INDUCTIGRAFT, were evaluated in vitro with STRO-1+ immunoselected human bone marrow derived mesenchymal stem cells (HBMSCs). Osteostimulative materials (Si-CaP) and Bioglass 45S5 (Bioglass) were also assessed as positive controls along with non-silicate substituted hydroxyapatite as a negative control.

Also assessed were HBMSCs on Thermanox (TMX) discs cultured in basal and osteogenic media to determine when osteogenic differentiation could be significantly detected with this in vitro cell system. HBMSC viability and necrosis, total DNA content, alkaline phosphatase (ALP) expression, and osteocalcin expression were evaluated after 7, 14, 21, and 28 days. It was demonstrated that INDUCTIGRAFT is osteostimulative based on its propensity to support STRO-1+ HBMSC proliferation.

The rationale for this study was to validate the osteostimulative potential of a new formulation of Si-CaP with enhanced porosity, Si-Cap EP, (INDUCTIGRAFT). Though Si-CaP and INDUCTIGRAFT have the same chemical composition, INDUCTIGRAFT has enhanced strut porosity which simulates the microporous osteocyte lacunae network present in physiological bone. To clarify, microporosity and strut porosity are used interchangeably. Strut pores are formed from the interconnected spaces existing between particles of calcium phosphate which have been sintered together to form the struts in the INDUCTIGRAFT scaffold. The term “strut porosity” is used to describe the pore volume fraction of each strut.

MATERIALS

- Five test articles were assessed in this study. Nunc Thermanox coverslips (Thermo Fisher Scientific: Waltham, MA, USA) with 13 mm diameter and 0.2 mm thickness were used as the control substrates to assess the basal versus osteogenic conditions.
- Bioglass 45S5 particles in a polyethylene glycol and glycerin carrier (Bioglass) were included as a positive control. Si-CaP, INDUCTIGRAFT, and hydroxyapatite (HA) implants were manufactured as described previously [19–21].
- Both Si-CaP and INDUCTIGRAFT consisted of porous, irregularly shaped microgranules (1–2 mm) of phase pure silicate-substituted calcium phosphate (0.8 wt% Si) in an aqueous poloxamer carrier.

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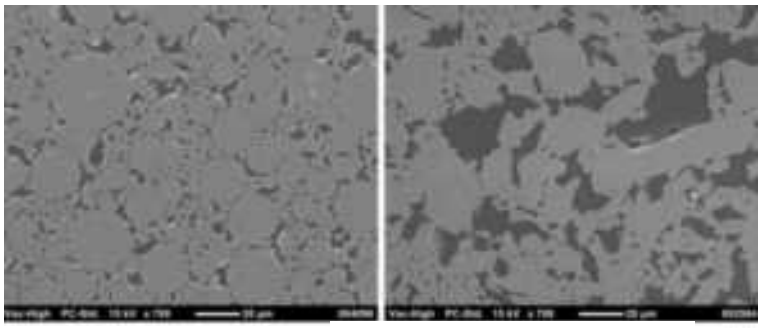
- The Si-CaP and HA granules had a mean total porosity of 80 % and a mean strut porosity of 22.5 %, while the Si-CaP EP granules had a mean total porosity of 82.5 % and a mean strut porosity of 39 %.
- Material characterization of chemical composition, density, total porosity, and strut porosity were measured as described in Campion et.al 2011.* Si-CaP and INDUCTIGRAFT granules were imaged Scanning Electron Microscopy to assess the differences in strut porosity.

RESULTS

- While both Si-CaP and INDUCTIGRAFT consists of porous 1–2 mm granules containing silicate-substituted calcium phosphate suspended in an aqueous gel carrier, they fluctuate in the amount of strut porosity which can only be detected on the microscopic level. Scanning Electron Microscopy images show that INDUCTIGRAFT has a greater amount of strut porosity in the 0.2–50-micron size range compared to Si-CaP. Figure 1

Figure 1 Scanned Electron Microscopy Images

Si-Cap EP (right) has great strut porosity compared to Si-Cap (left)



Si-CaP **Si-CaP EP**

- During the cell culture studies, all the test materials were easily controlled. After 2 hours of incubation, the test article carriers in Si-CaP, INDUCTIGRAFT, and Bioglass were dissolved. From the first day of culture until the 28th day (the longest time-point), the media from the Bioglass test group presented a fuchsia color which indicated a basic media. On the 21st day, the pH of all media was measured (Table 2). All groups except Bioglass presented a pH that was close to neutral pH, while the Bioglass media had a pH of 8.7. The HA group also presented a fuchsia color indicating a basic media, but only in the day zero samples. After the first media change, the color was characteristic of a pH between 6.8 and 8.2. Inversely, the media of Si-CaP and

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INDUCTIGRAFT had a tendency towards a yellow color on day 0, indicating a light acidity of the media. After the first media change, the color became normal.

Table 2 pH of media at day 21

Test article	pH at day 21
TMX basal control	7.7
TMX osteogenic control	7.9
HA	7.7
SiCaP	7.6
Bioglass	8.7
SiCaP EP	7.7

- **Cell Viability and Necrosis**
  Cells were evaluated with a live/dead cell assay. As the substrates prevented light transmission, it was challenging to properly visualize the cells given the opacity of the materials. A certain amount of the cells was able to be visualized in all treatments. The percentage of living cells compared with dead cells were classified from (-) to (+++) in this qualitative analysis. (Table 3)

Table 3 Viability/necrosis assay

Test article	Time point			
	7 days	14 days	21 days	28 days
TMX basal control	+++	+++	+++	+++
TMX osteogenic control	+++	+++	+++	+++
HA	+++	+++	+++	+++
SiCaP	+++	+++	+++	+++
Bioglass	++	++	++	++
SiCaP EP	+++	+++	+++	+++

(−) = 0 % of living cells, (+) = 0–40 % of living cells; (++) = 40–90 % of living cells; (+++) = >90 % of living cells

Total DNA:

- The DNA evaluation established a trend for increasing cell production in the TMX basal and osteogenic controls over the 28 day period (Fig.A)
- Considerably greater amounts of HBSMCs multiplying on INDUCTIGRAFT ($p < 0.05$) than HA at 7, 14, and 21 days were equivalent to 28 days (Fig. B)

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- The quantity of HBMSCs replicating on INDUCTIGRAFT was notably greater ($p < 0.05$) than Si-CaP at 7 and 14 days and was equal at 21 and 28 days. (Fig. C)
- There were substantially greater HBMSC proliferation on INDUCTIGRAFT ($p < 0.05$) than Bioglass at all timepoints. (Fig. D)

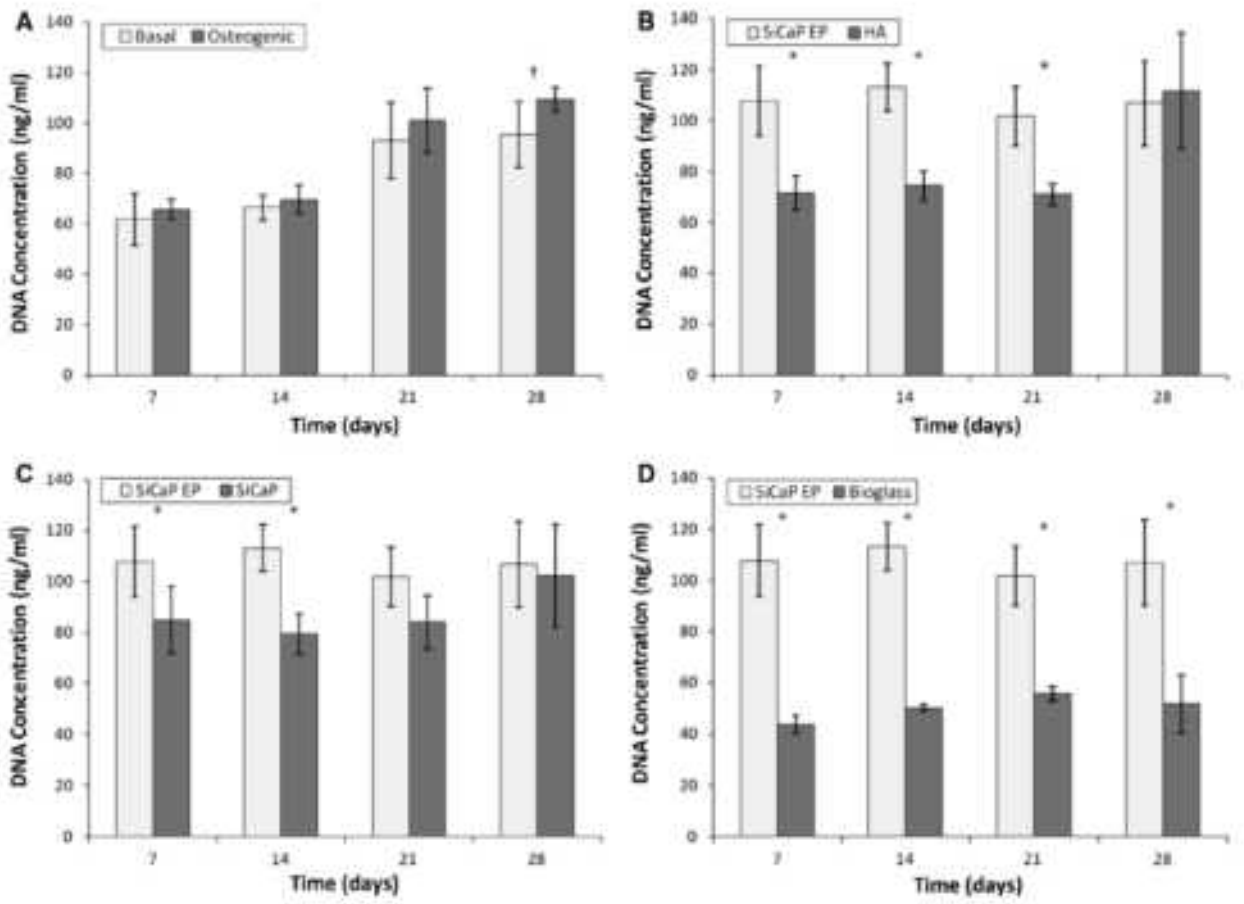

Fig. 2 DNA content comparing a TMX basal control versus TMX osteogenic control, b SiCaP EP versus HA, c SiCaP EP versus SiCaP, d SiCaP EP versus Bioglass (* $p < 0.05$, Mann-Whitney; † $p < 0.05$, student t test)

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- Fungal contamination occurred in various plates, primarily in the longer experiments. However, contamination did not occur in more than six wells in any plate. Therefore, the contamination did not compromise the experiment since the spare wells were available as replacements. Light microscopy images taken of the cultured plates after 14 days indicated that cells attached and spread over the TMX substrates. Conversely, the cells did not attach to the non-adherent tissue culture plastic in empty wells, rather the cells formed clumps which were suspended in the media.

CONCLUSIONS

INDUCTIGRAFT was able to promote the proliferation of an equivalent number of human bone marrow derived mesenchymal stem cells (HBMSCs) compared to the positive controls (Bioglass and Si-CaP) as demonstrated through cell DNA analysis. INDUCTIGRAFT promoted early-stage differentiation of HBMSCs as demonstrated through equivalent or better up-regulation of ALP expression compared to negative and positive controls.

INDUCTIGRAFT promoted late-stage differentiation of HBMSCs as demonstrated through upregulated production of Osteocalcin compared to the negative control and equivalent temporal up-regulation compared to the positive controls. INDUCTIGRAFT is osteostimulative based on its propensity to support HBMSC proliferation and promote the differentiation of HBMSCs down the osteoblastic lineage without the presence of external osteogenic factors from ALP-expressing, matrix-producing osteoblasts to osteocalcin-producing pre-osteocytes. The greater HBMSC attachment, ALP expression, and osteocalcin production in the INDUCTIGRAFT group compared to Bioglass could be attributed to its enhanced microstructure and chemistry.

*Campion C, Chander C, Buckland T, Hing K. Increasing strut porosity in silicate-substituted calcium-phosphate bone graft substitutes enhances osteogenesis. J Biomed Mater Res B. 2011;97(2):245–54.

Microstructure and Chemistry Affects Apatite Nucleation on Calcium Phosphate Bone Graft Substitutes Charlie R. Campion • Sara L. Ball • Daniel L. Clarke • Karin A. Hing Journal of Materials Science: Materials in Medicine Publisher: Springer US (NY) 3/13 –Vol. 24:Issue: 3 – pps. 597-610

INTRODUCTION

This study was completed to evaluate the Bioactivity of calcium phosphate bone grafts of fluctuating chemistry and strut-porosity by establishing the rate of formation of hydroxycarbonate apatite (HCA) crystals on the material surface and the degree to which these crystals formed after the material was saturated in simulated body fluid for time periods ranging from 3 to 30 days.

KEY HIGHLIGHTS

- The bioactivity of calcium phosphate bone grafts of varying chemistry and strut-porosity was compared by determining the rate of formation of hydroxycarbonate apatite crystals on the material surface after being soaked in simulated body fluid for up to 30 days.
- Three groups of silicate-substituted hydroxyapatite material were tested, with each group comprising a different quantity of strut-porosity (23, 32, and 46 % volume). A commercially available porous b-tricalcium phosphate bone graft substitute was tested for comparison.
- Results indicate that strut-porosity of a material affects the potential for formation of a precursor to bone-like apatite and further confirms previous findings that b-tricalcium phosphate is less bioactive than hydroxyapatite.

MATERIALS

Commercially available (ACTIFUSE Microgranules, ApaTech, Herts, UK) phase pure silicate-substituted (0.8 wt.% Si) hydroxyapatite (Si-CaP, Ca10(PO4)6(OH)2) material consisting of porous (80 ± 2.5 % total porosity), irregularly shaped microgranules (1–2 mm) with a strut-porosity of 22.5 ± 2.5 % (Si-CaP-23) was tested. Two additional groups of Si-CaP with strut-porosities of 32.0 ± 2.5 % and 46.0 + 2.5 % were also included in the study (Si-CaP-32 and Si-CaP-46 respectively). A commercially available (Vitoss Scaffold Morsels, Orthovita, USA) porous beta tricalcium phosphate (b-TCP, Ca3(PO4)2) bone graft substitute consisting of porous (90 % total porosity), irregularly shaped granules (1–4 mm) was tested alongside the silicate-substituted calcium phosphate treatment groups.

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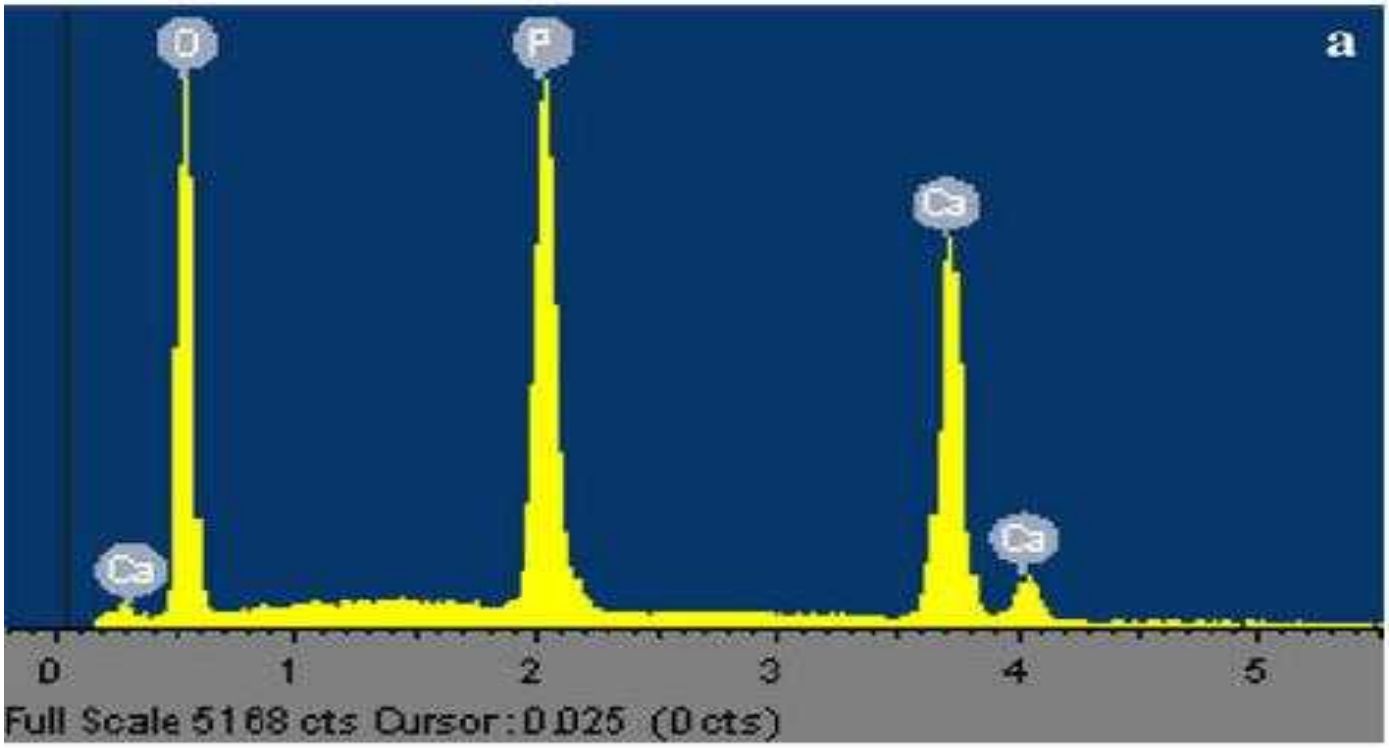
RESULTS

Energy dispersive X-Ray analysis When compared to spectra for synthesized HCA (Fig. 1a) and untreated specimen containers (Fig. 1b) no calcium or phosphorus was detected on polypropylene specimen containers following exposure to SBF for 30 days (Fig. 1c). Carbon and Oxygen were detected in expected quantities for a polypropylene material in addition to the Platinum-Palladium coating.

Scanning electron microscopy

Scanning electron microscopy found there was no evidence of spontaneous formation of HCA crystals on the surface of the polypropylene containers in which the materials were tested. This was established by comparing samples from un-tested container with material from containers in which samples had been aged for 30 days. (Figs. 2a-c)



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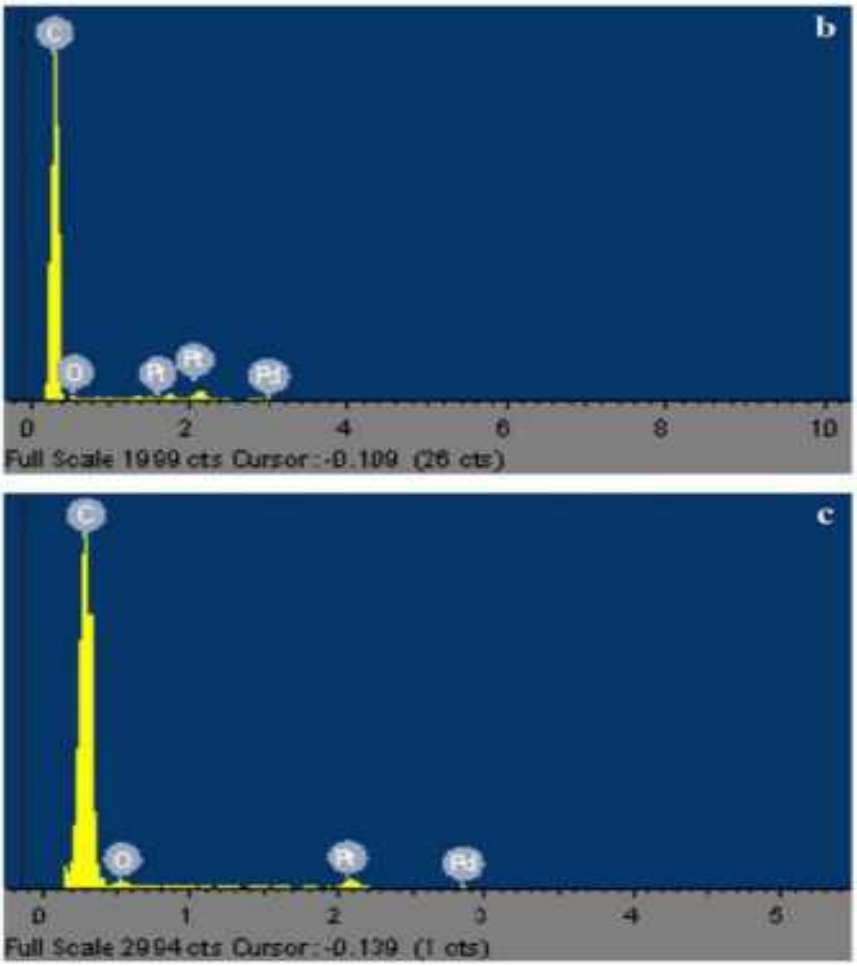

Fig. 1 Energy Dispersive X-Ray spectra for **a** synthesised carboxy-apatite. **b** untreated polypropylene specimen containers and **c** polypropylene containers following exposure to SBF for 30 days

Evidence of carbonate apatite formation was observed on the surface of all test materials as early as day 3 after being immersed in SBF. The mode of HCA formation for Si-CaP-23; Si-CaP-32; and Si-CaP-46 was consistent between test groups. Formation of the HCA layer covered the entire surface of the material after only 3 days and was not localized to any one surface artefact

Microstructure and Chemistry Affects Apatite Nucleation on Calcium Phosphate Bone Graft Substitutes Charlie R. Campion • Sara L. Ball • Daniel L. Clarke • Karin A. Hing Journal of Materials Science: Materials in Medicine Publisher: Springer US (NY) 3/13 –Vol. 24:Issue: 3 – pps. 597-610

Inductively coupled Plasma Optical Emission Spectrometry

There were no considerable differences in Silicon concentration over the 30 days of the study for any treatment group. There were substantial reductions in both Calcium and Phosphorus ions in the SBF from 0 to 30 days for all treatment groups. There appeared to be a greater decline in both ions for the Si-CaP groups than the b-TCP group after 30 days immersion. The amount of fluctuation in ion levels over the course of the experiment was noted.

However, between days 6 and 9 Ca ion concentrations increased in SBF solutions in which Si-CaP-23 and Si-CaP-32 were incubated but continued to decrease in SBF solutions incubated with either Si-CaP-46 or b-TCP and the Phosphorus concentrations of SBF solutions in which Si-CaP-23; Si-CaP-32; and b-TCP were incubated increased but decreased for Si-CaP-46. Between days 9 and 14 both Calcium and Phosphorus ions decreased in concentration for all treatment groups apart from b-TCP. After 18 days there was a continued loss of Calcium and Phosphorus ions from all solutions.

CONCLUSIONS

The propensity for the formation of either HCA or OCP as a continuous, un-broken layer over the implant surface immediately after implantation into bone is in theory likely to be significant to the processes of osteointegration; the greater the surface area covered by this layer the greater the opportunity for interaction with osteogenic proteins and development of a graduated interlayer between organic and inorganic phases, and consequently the better the opportunity for interdigitation with host bone.

In practice this assumption is still under debate as the in vivo studies in support of the outcomes of the Bioactivity test are often contradictory. In our study, INDUCTIGRAFT exhibited the fastest rate of HCA growth compared with less porous Si-Cap formulations. When immersed in simulated body fluid, Vitoss ((β-tricalcium phosphate) is less bioactive than silicate hydroxyapatite and less likely to facilitate successful osseointegration when implanted in bone.

The rates of formation and quantities of HCA varied among different materials. Under the conditions of the test, the fastest rate of HCA growth was observed on Si-CaP-32 and Si=CaP-46 followed by Si-CaP-23. The quantity of HCA formed on the b-TCP surface was much lower than the other three test materials.

These results indicate that the strut-porosity of a material substrate should be increased to maximize the potential for formation of a precursor to bone-like apatite after implantation in osseous defects and further confirms previous reports that b-TCP is less Bioactive than silicate-substituted hydroxyapatite and thus less likely to facilitate successful osteointegration when implanted in bone.

Evaluation of a Novel Silicate Substituted Hydroxyapatite Bone Graft Substitute in a Rabbit Posterolateral Fusion Model Douglas C Fredericks, Emily B. Petersen, ikhil Sahai, Katherine Gibson N. Corley, Nicole DeVries, Nichole M. Grosland, Joseph D. Smucker The Iowa Orthopaedic Journal, ABSTRACT, Vol 33, pps. 25-32

INTRODUCTION

Even though Iliac crest autograft (ICBG) is considered the "gold standard" graft material in spine surgical techniques, its limitations include the lack of quantity and known complications when harvesting it. Clinicians continue to search for alternative graft materials to extend, enhance and/or substitute for ICBG.

This study was to determine performance characteristics between a novel silicate-substituted hydroxyapatite bone graft substitute (BGS), SiCap EP (INDUCTIGRAFT), in a stand-alone mode, a stand-alone with bone marrow aspirate (BMA) and an extender mode with ICBG in a rabbit posterolateral spine fusion model. The investigational BGS is compared to a standard ICBG control.

MATERIALS

Using the rabbit fusion model in evaluating INDUCTIGRAFT, three groups were compared with autograft (2.5cc/side volume). Trial groups were distributed as follows:

- Inductigraft stand-alone group (2.5 cc/side volume)
- Inductigraft stand-alone group with BMA 1:0.5 by volume (2.5 cc Inductigraft + 1.25 cc BMA)
- Iliac crest autograft extender group with Inductigraft 3:1 by volume (2.0 cc ICBG + 0.5 cc Inductigraft)

Table 1 outlines the Experimental Design

Table 1: Experimental Design

Group	Total Animals per Time Point	Plain Radiograph and pqCT (n per time point)	Manual Palpation and Mechanical Testing (n per time point)	Histopathology / Histomorphometry (n per time point)	Time Points
Autograft (ICBG)	10	5	10	5	4, 8, and 12 weeks
ICBG + SiCaP EP (1:1)	10	5	10	5	4, 8, and 12 weeks
SiCaP EP	10	5	10	5	4, 8, and 12 weeks
SiCaP EP + BMA (1:0.5)	10	5	10	5	4, 8, and 12 weeks

METHODS

Surgical Procedure: This surgical model was a single-level lumbar intertransverse (posterolateral) fusion at L5-L6. This surgical approach was identical in all rabbits.

Radiographic Assessment: Rabbits were radiographed preoperatively, at the time of euthanasia. Radiographic images were obtained at time zero and at 4, 8 and 12 weeks post-surgery.

Necropsy: The rabbit's entire lumbar columns were removed "en-bloc".

Macroscopic Evaluation of Paraspinal Bed: Soft tissues were immediately removed from the surgically treated spinal unit after the spine was dissected out of the body. Graft migration, infection and soft tissue abnormalities were examined from the grafted site.

Manual Palpation: Final results were concluded by an agreement of at 2 of the 3 observers on:

- Stiffness of the fused motion assessed by manual palpation
- "Fused" if no detectable motion at the disc space was detected in flexion and extension
- "Not fused" if motion was present

Mechanical Testing: Biomechanical non-destructive stiffness testing was performed following manual palpation. Testing consisted of flexion/extension, lateral bending, and torsion to a pre-determined, sub-failure load. Nondestructive flexibility tests were performed about each axis of rotation (i.e., flexion-extension, right-left lateral bending, and right-left axial rotation) by applying an isolated $\pm$0.27 Nm moment about each of the primary axes.

Each test initiated and concluded in the neutral position with zero load. Three loading and unloading cycles were performed with motion data collected on the third cycle (the first two cycles served as preconditioning). Stiffness was determined and compared to normal controls (10 normal rabbit lumbar columns, historic internal laboratory controls).

Histology: Six non-decalcified resin embedded samples from five animals in each group and at each time point were evaluated for histomorphometry (N=3 sections per fusion mass). Histology slides from each fusion mass were stained with hematoxylin and eosin and evaluated with MicroSuite Pathology Edition software, Olympus, and Image J. NIH the total area (TA) and bone area (BA) were evaluated for each slide. The areas from six slides of each animal were averaged to obtain a single mean TA and BA value for each animal. These values were used to calculate the normalized bone area percentage (BA/TA)*100).

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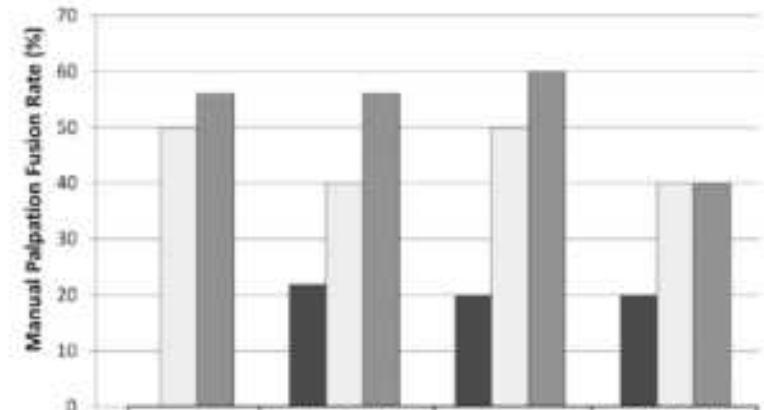
Statistical Analysis: Statistical analysis was performed on the flexion-extension flexibility data as well as the normalized histomorphometric bone area percentages. First, a normality test was performed on each data set from each time point. If the data was normal, a student's t test was conducted (a=0.05). If the data was not normal, a non-parametric Mann=-Whitney test was used (a=0.05).

RESULTS

Radiology: Density of the implanted test articles made analysis of continuous trabecular bone formation in the test article groups challenging. No fractures, osteolysis, or other adverse reactions were evident during radiographic examination.

Necropsy/Macroscopic Examination: Necropsy of the animals that completed the scheduled time courses was ordinary regardless of treatment. Macroscopic analysis of the graft site established healthy tissue with no noticeable adverse effects such as inflamed, necrotic, or devascularized tissue surrounding the operated levels.

Manual Palpation Assessment of Fusion: Fusion was assessed by manual palpation of the treated motion segment (Figure 1). The fusion rate by manual palpation for ICBG in the current study (0%, 50%, and 56% at 4, 8 and 12 weeks respectively) is consistent with results from previous studies as well as consistent with the radiographic result in this study. At 8 and 12 weeks, all five implant groups obtained fusions in approximately half of the specimens, thus no variance between the test groups were detected.



	ICBG	ICBG + SiCaP EP (3:1)	SiCaP EP	SiCaP EP + BMA (1:0.5)
4 weeks	0% (0/9)	22% (2/9)	20% (2/10)	20% (2/10)
8 weeks	50% (5/10)	40% (4/10)	50% (5/10)	40% (4/10)
12 weeks	56% (5/9)	56% (5/9)	60% (6/10)	40% (4/10)

Figure 1: Manual Palpation Fusion Rates

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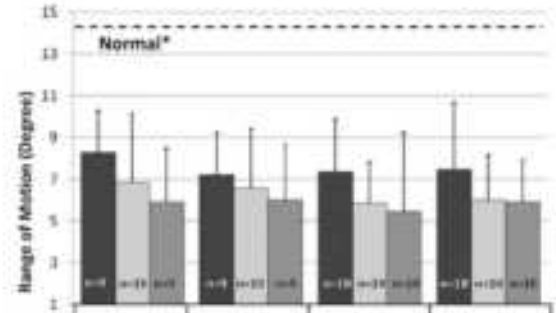
Mechanical Testing Stiffness: Motion in the flexion/extension plane was used as the primary measurement to demonstrate fusion as manual palpation testing is based off of motion detected in flexion/extension (Figure 2). It was concluded that the flexion/extension data at 4, 8 and 12 weeks was not normally distributed, thus a non-parametric Mann Whitney test was used to determine statistically noteworthy differences at a=0.05.

General findings from the biomechanical analysis indicate that the five groups had similar performance to each other and had statistically significantly less range of motion compared to the normal controls at each time period.



	ICBG	ICBG + SiCaP EP (3:1)	SiCaP EP	SiCaP EP + BMA (1:0.5)
4 Weeks	8.27 ± 2.00	7.18 ± 2.03	7.35 ± 2.54	7.46 ± 3.21
8 Weeks	6.84 ± 3.31	6.56 ± 2.85	5.83 ± 1.98	5.98 ± 2.16
12 Weeks	5.91 ± 2.55	6.00 ± 2.63	5.42 ± 3.80	5.91 ± 2.03

* Baseline normal data obtained from historical internal laboratory data of normal unfused rabbits

Figure 2: Mean Maximum Flexion/Extension Motion at 0.27Nm with Standard Deviation (Mean ± Standard Deviation)

Histopathology: The majority of these specimens, regardless of implant type or time of implantation had low to moderate multifocal to coalescing inflammation throughout the implantation site, primarily composed of lymphocytes and plasma cells with fewer macrophages and multinucleated giant cells. The implant sites were composed of bone and fibrous connective tissue which was more mature in the 8-12 week animals as compared to the 4 week animals. Also present within implant sites, were variable amounts of new cartilage. The fibrous tissue appeared to differentiate into either new cancellous bone (membranous ossification) and/or cartilage. Within the fibrous connective tissue there was moderate neovas-cularization. TRAP staining revealed mild to moderate osteoclastic activity near and around the residual implant indicating resorption of the graft material (Figure 3).

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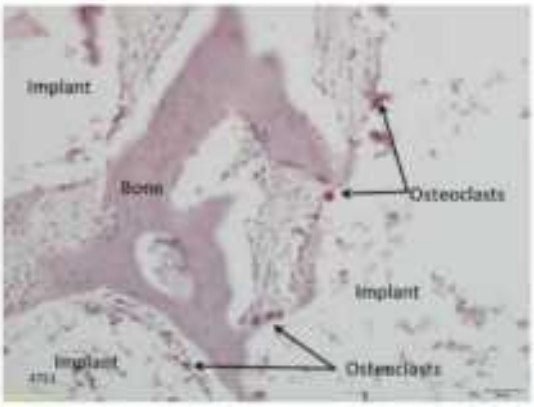

Figure 3: Decalcified histology section of SiCaP EP at 8 weeks with TRAP staining indicating presence of osteoclasts on the graft surface (12.6x magnification)

Histomorphometry: There were no adverse inflammatory reactions seen in any of the non-decalcified plastic embedded histology sections, regardless of graft type. The majority of sections within each group had new woven bone dorsal to the transverse processes in direct apposition or within the graft. Islands of new bone were evident within the center of the graft in all groups. Representative non-decalcified plastic embedded histology sections at 12 weeks are presented in Figures 4-7.

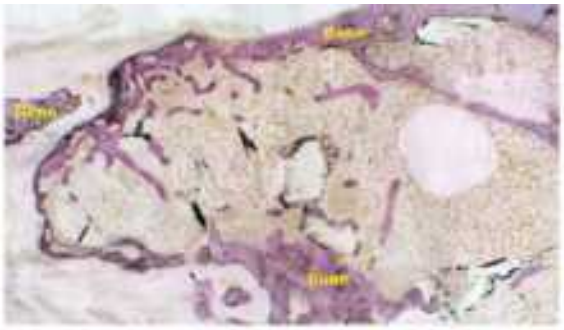

Figure 4: Non-decalcified histology section of ICBG at 12 weeks: H&E staining (1.26x magnification)

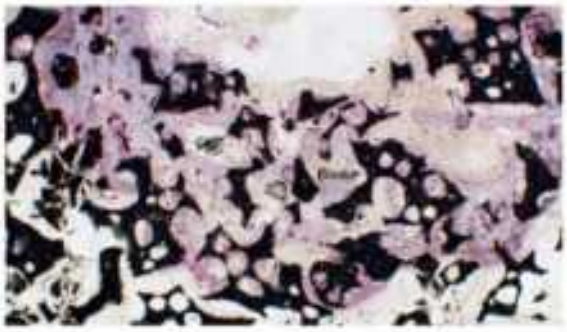

Figure 5: Non-decalcified histology section of ICBG+SiCaP EP (3:1) at 12 weeks: H&E staining (1.26x magnification)

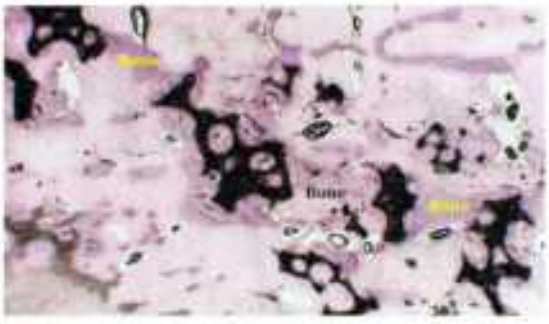

Figure 6: Non-decalcified histology section of SiCaP EP at 12 weeks: H&E staining (1.26x magnification)

Figure 7: Non-decalcified histology section of SiCaP EP+BMA (1:0.5) at 12 weeks: H&E staining (1.26x magnification)

Normalized bone area percentages are provided in Table 3. A bar chart of the mean data with standard deviations is provided in Figures 8. It was determined that the 4 week normalized bone area data was not normally distributed, thus this data set was statistically assessed using a non-parametric Mann-Whitney test (α=0.05). The remaining data sets were normally distributed and were assessed with a student t-test (α=0.05). Statistical analysis of the histomorphometric normalized bone area percentages is presented in Table 4.

At 4 and 8 weeks, ICBG had greater normalized bone area compared to all other groups. At 12 weeks, all groups had equivalent normalized bone area, indicating all test groups demonstrated equivalent bone healing to ICBG.

Table 3: Normalized Histomorphometry Area Percentages (Mean ± Standard Deviation)

	Time Point	(No. Fused/ Total No.)	Normalized Bone Area (BA/TA) %
ICBG	4	(0/5)	37.333 ± 5.948
ICBG + SiCaP EP (3:1)	4	(1/5)	29.056 ± 6.103
SiCaP EP	4	(1/6)	24.400 ± 4.519
SiCaP EP + BMA (1:0.5)	4	(1/5)	19.533 ± 1.321
ICBG	8	(3/5)	34.656 ± 4.358
ICBG+SiCaP EP (3:1)	8	(2/5)	27.139 ± 4.969
SiCaP EP	8	(2/5)	25.400 ± 1.663
SiCaP EP + BMA (1:0.5)	8	(2/5)	24.933 ± 5.084
ICBG	12	(2/5)	25.744 ± 2.904
ICBG + SiCaP EP (3:1)	12	(3/5)	26.500 ± 2.650
SiCaP EP	12	(2/5)	25.856 ± 4.600
SiCaP EP + BMA (1:0.5)	12	(2/5)	24.100 ± 1.525

Table 4: Statistical Analysis of Normalized Bone Area Measured with Histomorphometry (p value from student t-test / [p value from non-parametric Mann-Whitney test])

	ICBG + SiCaP EP (3:1)	SiCaP EP + BMA (1:0.5)	SiCaP EP
4 Week Data			
ICBG	[0.095]	[0.012]	[0.022]
ICBG + SiCaP EP (3:1)		[0.012]	[0.175]
SiCaP EP + BMA (1:0.5)			[0.037]
8 Week Data			
ICBG	0.028	0.014	0.007
ICBG + SiCaP EP (3:1)		0.490	0.452
SiCaP EP + BMA (1:0.5)			0.855
12 Week Data			
ICBG	0.680	0.305	0.965
ICBG + SiCaP EP (3:1)		0.130	0.795
SiCaP EP + BMA (1:0.5)			0.463

CONCLUSIONS

As evidenced through multiple metrics in this model, the results of this study indicate that INDUCTIGRAFT is effective in producing posterolateral fusion when employed as a bone graft substitute. Examination into the use of INDUCTIGRAFT as a BGS in a clinical setting may be applicable to further characterize its efficacy, although animal models cannot be directly translated to clinical application.

SiCaP EP utilized as a stand-alone, as a stand-alone with BMA, and as an autograft (ICBG) extender demonstrated equivalent fusion rates, stiffness and normalized bone area compared with ICBG at 12 weeks in this rabbit posterolateral fusion model.

INDUCTIGRAFT, ICBG+INDUCTIGRAFT (3:1) and INDUCTIGRAFT+BMA (1:0.5) compares favorably to autologous iliac crest bone graft by multiple metrics in this rabbit posterolateral fusion model.

The Effect of Microporosity on Osteoinduction of Calcium Phosphate Bone Graft Substitute Biomaterials O. Chan, M.J. Coathup .A. Nesbitt , C.-Y. Ho, K.A. Hing , T. Buckland , C. Campion, G.W. Blunn Acta Biomaterialia 8 (2012) pps: 2788-2794

INTRODUCTION

An Ectopic ovine model was used to examine the effect of increasing strut porosity on the osteoinductive ability of ACTIFUSE (silicate substituted calcium phosphate, or Si-CaP). The premise of this analysis is to determine whether ACTIFUSE, with increased strut porosity, would display greater osteoinductivity at earlier time points.

MATERIAL AND METHODS

ACTIFUSE materials were irregularly shaped granule-based preparations, phase pure and had identical chemical composition and ultra-microporous morphological structure. Materials from all treatment groups had the same total macroporosity and an average macropore diameter but varied in their microporous structure and levels of strut porosity. (Table 1)

Table 1
SiCaP bone graft substitute materials: strut porosity by percentage volume as measured by optical microscopy and image analysis.

Implant	Granule size	Strut porosity (with standard error bars)	Comments
SiCaP 22.5	1–2 mm	22.5 ± 2.5%	Dry granules
SiCaP 32	1–2 mm	36.0 ± 2.5%	Dry granules
SiCaP 46	1–2 mm	47.0 ± 2.5%	Dry granules

Implants were inserted into the paraspinalis muscle of 18 female, commercially crossbred sheep weighing between 60 and 80 kg and between 2 and 5 years of age. These implants with strut porosities of 22.5%, 32.0%, and 46.0% that had the histological section prepared at the clinically relevant timepoints of 8, 12, and 24 weeks. These sections were then studied using backscattered scanning electron microscopy and undecalcified histology. The bone and implant area as bone-implant contact were measured.

- Bone formation within ACTIFUSE material was measured by the selection of seven random regions of interest along the length of the implant. To quantify bone formation, a line intercept method was used within each histological image.
- A mask of interconnecting lines measuring 10 x 12 mm was placed over each image and the mineralized bone, soft tissue, or implant material at the intersection of each line was determined for a total of 225 intersect points per image.
- Percentage of bone was based on the overall area of the implant site.

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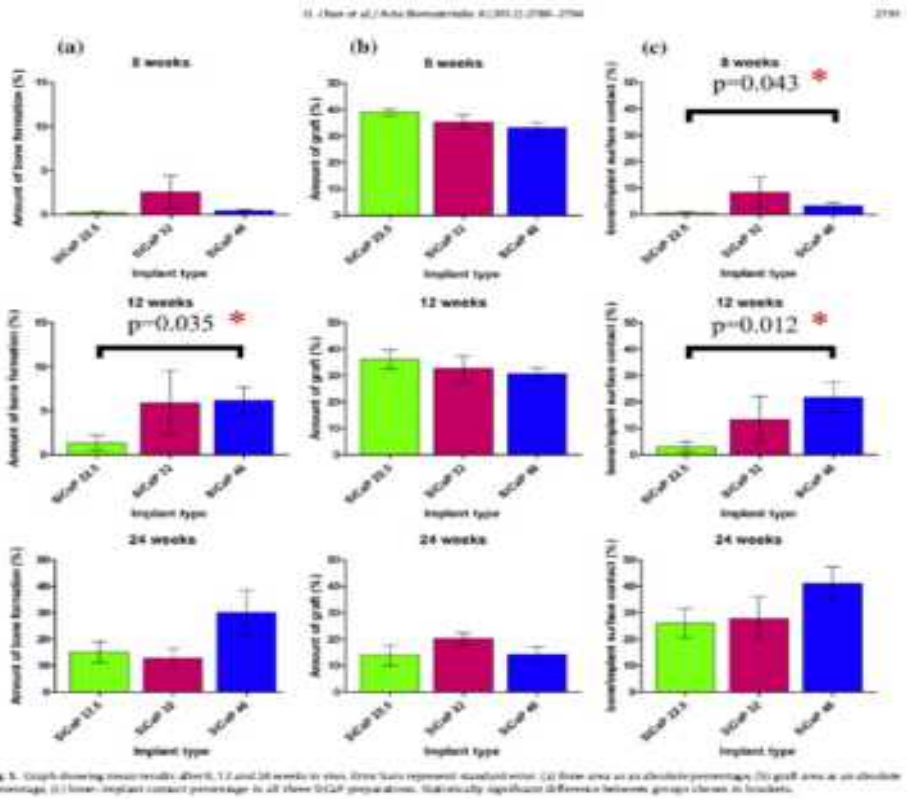
- Percentage of bone-implant contact was also verified at the points where lines intersected with the ACTIFUSE biomaterial surface.

RESULTS

NEW BONE FORMATION: ACTIFUSE material was able to generate the formation of bone in ectopic sites as early as 8 weeks. A maximum of only 2.56% was seen in ACTIFUSE scaffolds at this time. Though no substantial difference was found when all 3 groups were compared at 8 weeks post implantation. Results (with standard error) were as follows:

- ACTIFUSE-22.5 (0.20 ± 0.15%)
- ACTIFUSE-32 (2.56 ± 1.86%)
- ACTIFUSE-46 (0.44 ± 0.12%)

At 12 weeks, results showed noteworthy increased amounts of new bone formation were observed in the ACTIFUSE-46 Group (6.17 ±1.51%) compared with the ACTIFUSE-22.5 group (1.33 ± 0.84%, *p=0.035*). Fig. 1



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LIGHT MICROSCOPY

8 weeks: Bone formation seen forming predominantly arranged concentrically adjacent to the concave surface of the biomaterial within the macropores of the implant

12 weeks: Bone formation observed more uniformly distributed within the implant with areas of osteogenesis detected (Fig. 2)

24 weeks: Bone marrow observed within some of the macropores specimens.

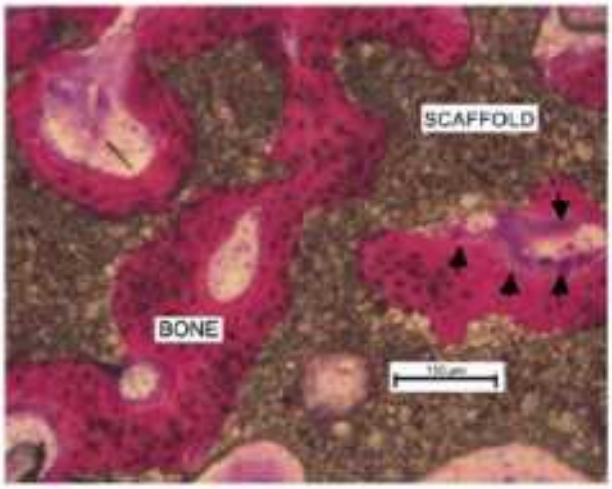

Fig. 2. Photomicrograph showing bone formation in a SiCaP-46 sample after 12 weeks in vivo. Bone growth is seen bridging scaffold granules together and an area of osteogenesis within a macropore observed (identified by arrows). Stain: Paragon and Toluidine Blue. Magnification: ×10.

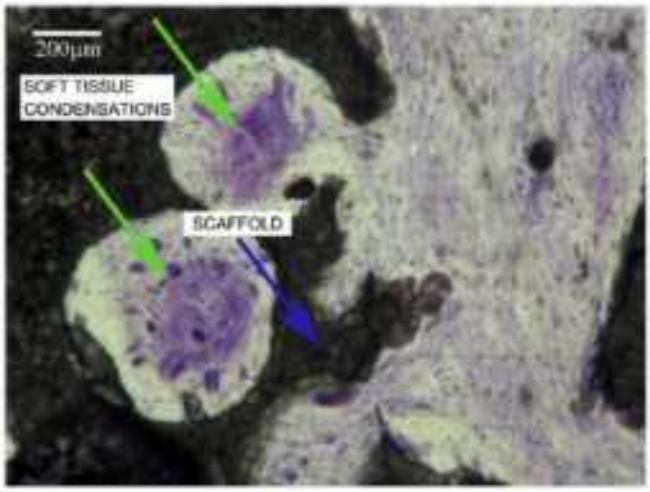

Fig. 3. Photomicrograph of a SiCaP-22.5 scaffold at the 8 week time point showing soft tissue concentrations within implant macropores. These soft tissue areas stained densely with Toluidine Blue. Magnification: ×10.

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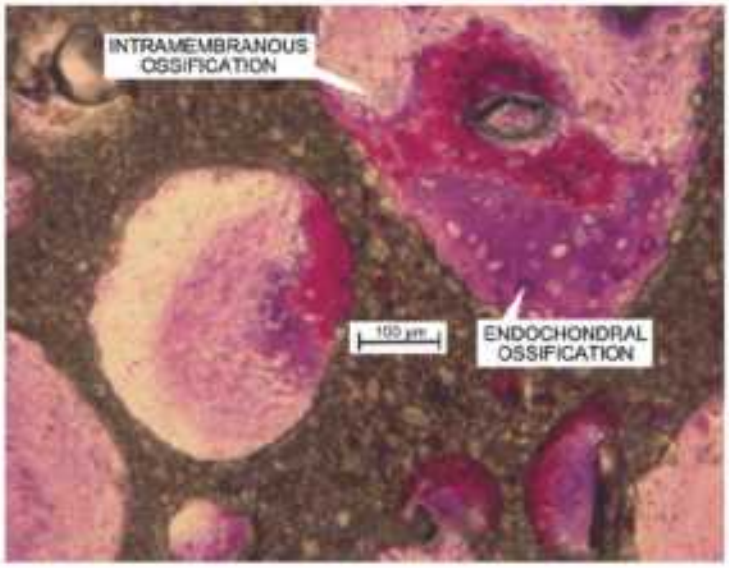

Fig. 4. Photomicrograph of a histological image taken from an SiCaP-46 sample 12 weeks post-implantation showing bone formed by both intramembranous and endochondral ossification. Stain: Paragon and Toluidine Blue. Magnification: ×10.

In some of the 8 week specimens, dense pockets of soft tissue, stained strongly with Toluidine Blue, were observed within the center of the macropores and these regions were associated with thick collagen fibers (>10 µ in diameter) which appeared to be organized in relation to the implant surface (Fig. 3). The regions of densely stained tissue were not detected in contact with the edge of the bone graft substitute adjacent to the muscle bed. Within all groups, and predominantly in the 12-week specimens, bone formed by both intramembranous and endochondral ossification, often within close proximity to one another. (Fig. 4)

The increased significance in bone-implant contact observed at 8 and 12 weeks in ACTIFUSE-46, compared with ACTIFUSE-22.5 implies that great strut porosity resulted in greater osteoconduction.

CONCLUSION

The results substantiated the premise that ACTIFUSE with increased strut porosity displays greater osteoinduction at earlier time points. This study emphasized a further variable in the development of an excellent bone graft substitute material. Additional work is required to interpret whether further increases in strut porosity are advantageous in improving osteoinduction. Structural integrity of the graft material may be compromised by too high strut porosities.

Increasing Strut Porosity in Silicate-substituted Calcium-phosphate Bone Graft Substitutes enhances Osteogenesis Charlie R. Campion, Chaman Chander, Tom Buckland, Karin Hing Journal of Biomedical Materials Research B: Applied Biomaterials- 2011; Vol. 97B, Issue 2: pps: 245-254

INTRODUCTION

There have been several studies concentrating on obtaining adequate materials that can closely imitate the chemical composition and structure of bone. The fundamental uniqueness of synthetic bone graft materials is essential to the extent to which they can produce a positive cellular response to their implantation. The micro-environment within the graft seems to encourage the process of osteogenesis.

This study was created to explore the potential benefits of increasing the strut porosity in synthetic bone graft substitutes on osteogenesis in an ovine critical-sized intraosseus defect model. There were 2 studies completed:

Study A: To substantiate the ovine critical defect model and its capacity for repair using microporous synthetic bone graft substitutes. The biological response of empty defect (control) sites was compared with bone graft materials consisting of a porous silicate-substituted HA matrix (ACTIFUSE; 0.8 wt% Si) that has previous been proven to be effective in healing osseous defects in lapine and ovine models when compared with HA.

Study B: Study scrutinized the biological responses and graft stability to different test graft materials that comprised of Si-CaP matrices (0.8 wt% Si) with varying interconnected strut porosity ranging from 32% to 46%.

METHODS

Study A: Conducted to authenticate the intraosseous implantation of Si-CaP (ACTIFUSE) materials with a strut porosity level of 23% into the distal femoral epiphyses of sheep (*Ovis aries*) and compared the healing of the defect site with nonimplanted empty defect (control) sites.

Study B: Evaluated the intraosseous implantation of Si-CaP test material with strut porosity levels of 32% or 46% using the same ovine model as Study A.

- Sheep were euthanized at either 8 or 12 weeks and samples were retrieved for evaluation using histological analysis and micro-computerized tomography for both studies.
- Fifty-four skeletally mature adult ewes between 2 and 5 years old, Study A: n=18, Study B n=36), underwent bilateral surgery on the distal femur with 2 defects being generated on each side of the femur. In both studies, the locations in which synthetic bone graft materials were implanted and the allocation of animals to treatment groups were conducted according to randomization schedules that were created prior to the start of the surgical procedures.
- Defects were filled with test formulations with the graft material being in close contact with all internal surfaces of the defect or left empty in control operations. Filling was completed by gradually loading from bottom to top and the test formulations were gently packed down with a metal spatula to not damage the brittle porous granules. Incisions were closed by suturing both capsule and muscles with absorbable thread.

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RESULTS

Study A – Histology Findings

Histological evidence of creeping edge repair in untreated (control) defects and no bone tissue in the center at 8 weeks [Figure 1(a)]

Osseous repair was observed in the center of the defect and characterized by regions of centripetal bone growth within the macropores [Figure 1(b)].

The empty (control) sites continued to show signs of poor bone regeneration at 12 weeks with no evidence of bone in-growth in the center of the defect validating this size of defect as being critically sized and an appropriate test control under the conditions of the study [Figure 1(c)].

At both 8 and 12 weeks, the level or volume apposition appeared similar for Si-CaP-23G and Si-CaP-23P. Figure [1 (b,d)].

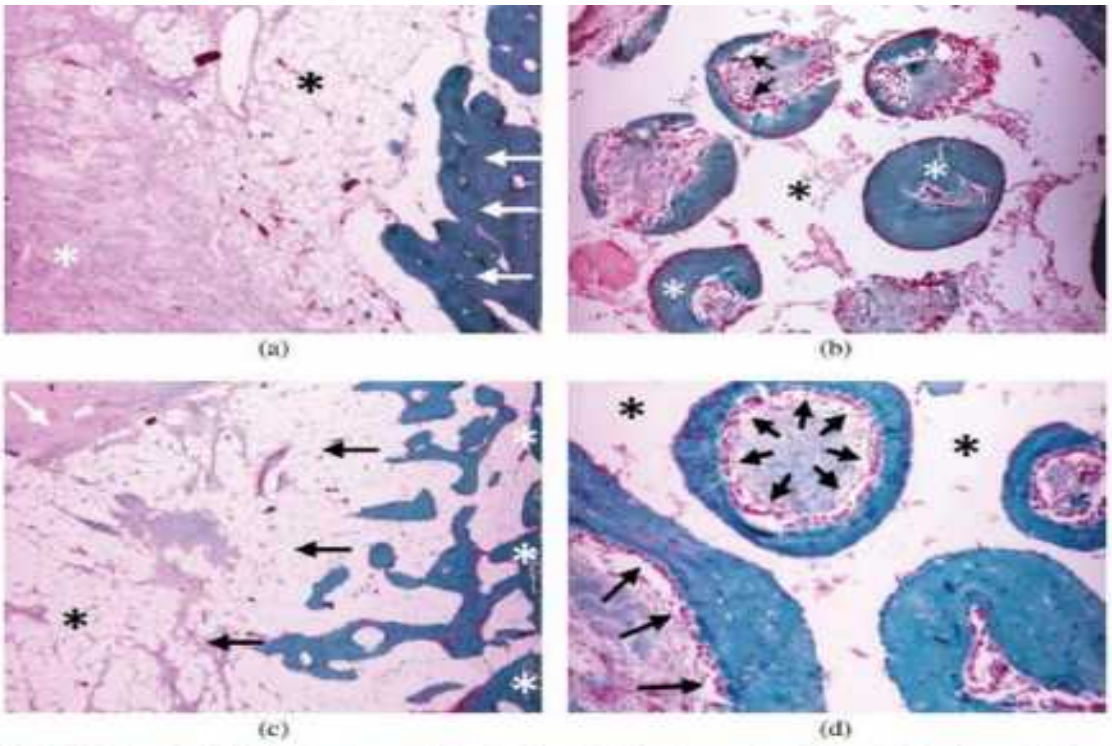
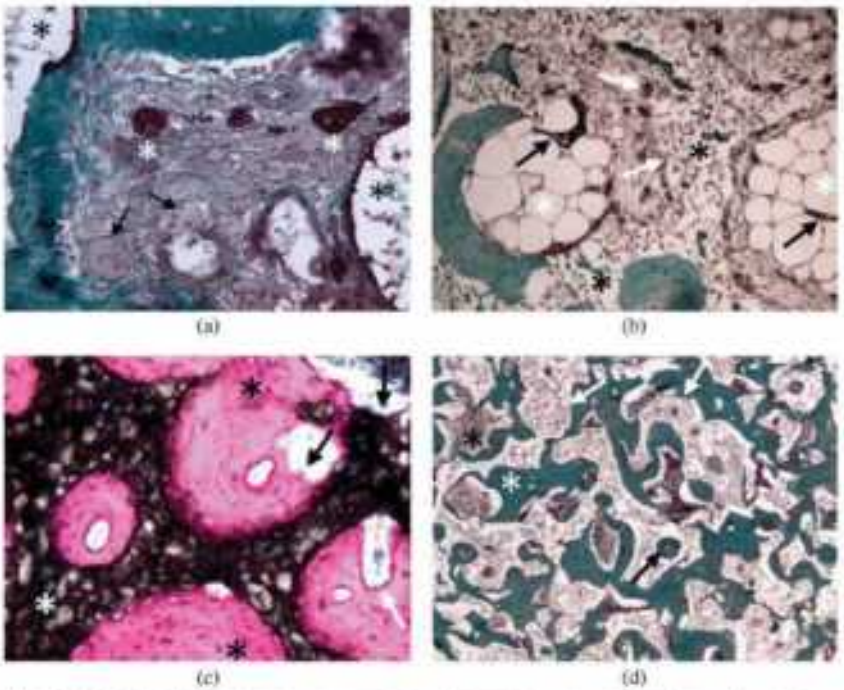


FIGURE 1. (a) Control ×2 Mag Masson's trichrome staining. Paraffin-embedded histology specimen (×2 magnification; Masson's trichrome stain) for an empty (nonimplanted) control defect at eight weeks, showing early signs of creeping edge repair (white arrows). The center of the defects were filled with fibrous tissue (white asterisk) and bone marrow (black asterisk). (b) SiCaP-23P × 10 Masson's trichrome staining. Paraffin-embedded histology specimen (×10 magnification; Masson's trichrome stain) for SiCaP-23P at eight weeks showing bone growth (white asterisks) throughout the implanted material (black asterisk) in the center of the defect after eight weeks implantation. Woven bone formed centripetally in the macropores of the material (black arrows). (c) Control ×2 Mag Masson's trichrome staining. Paraffin-embedded histology specimen (×2 magnification; Masson's trichrome stain) for an empty (nonimplanted) control defect at 12 weeks, showing creeping edge repair at the edges of the defect (white asterisks) towards the center of the defect (black arrows). The center of the defects were filled with fibrous tissue (white arrow) and bone marrow (black asterisk). (d) SiCaP-23G × 10 Mag Masson's trichrome staining. Paraffin-embedded histology specimen (×10 magnification; Masson's trichrome stain) for SiCaP-23G (black asterisk) at 12 weeks, showing centripetal bone growth in direct apposition to the material surface by osteoblasts (black arrows).

Increasing Strut Porosity in Silicate-substituted Calcium-phosphate Bone Graft Substitutes enhances Osteogenesis Charlie R. Campion, Chaman Chander, Tom Buckland, Karin Hing Journal of Biomedical Materials Research B: Applied Biomaterials- 2011; Vol. 97B, Issue 2: pps: 245-254

Study B:

- At 8 weeks, test materials demonstrated presence of a neo-vascular network penetrating into the center of the defect similar to that observed with the Si-CaP-23 material, but appearing more established in the higher strut porosity (32-46%) test materials [Figure 2 (a,b)]
- Mild inflammatory response was also observed consistent with that observed for Si-CaP-23 [Figure 2(a)].
- In all 4 test materials, bone apposition was well advanced with evidence of cell-mediated remodeling [Figure 2 (b,c)] and the characteristic centripetal bone growth with direct apposition of woven bone onto SiCap granule macropore surfaces [Figure 2(c)].
- Structural morphology of new bone appeared most advanced with Si-CaP-46G vs. other components of Study B; with evidence of direct apposition of lamellar bone within central regions of the defect and a more interpenetrating network of new bone within the graft macroporosity [Figure 2(d)]
- Neovascularization more established with higher strut porosity



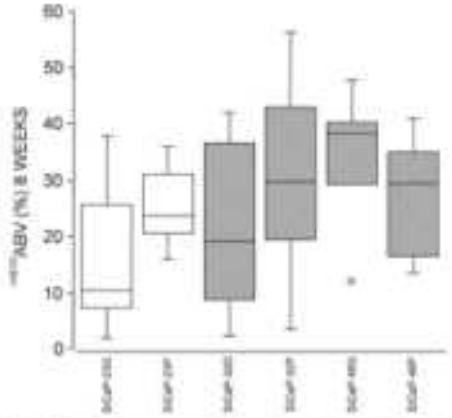
Increasing Strut Porosity in Silicate-substituted Calcium-phosphate Bone Graft Substitutes enhances Osteogenesis Charlie R. Campion, Chaman Chander, Tom Buckland, Karin Hing Journal of Biomedical Materials Research B: Applied Biomaterials- 2011; Vol. 97B, Issue 2: pps: 245-254

HISTOMORPHOMETRY RESULTS

At 8 weeks, the histomorphometry of graft treated defect sites demonstrated an inclination towards greater mean values for the volume of newly formed bone (^{HISTO}ABV) in the higher strut porosity graft treated defect sites, but the differences did not achieve statistical significance ($p>0.05$ for all comparisons **(Figure 4)**

There were no significant differences in the ^{HISTO}ABV of Si-CaP-23G and Si-CaP-23P treated defect sites at 12 weeks after implementation. **(Figure 5)**

In comparison, graft materials with higher strut porosity (32-46%) demonstrated statistically considerably higher ^{HISTO}ABV values that those for Si-CaP-23G and Si-CaP-23P ($p <0.05$) in all cases. **(Table II)**



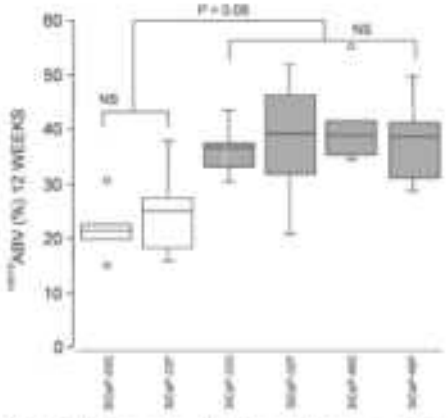


TABLE II. Histomorphometric Results

	Mean ^{HISTO}ABV (SD)					
	SiCaP-23G (n = 6)	SiCaP-23P (n = 6)	SiCaP-32G (n = 6)	SiCaP-32P (n = 6)	SiCaP-46G (n = 6)	SiCaP-46P (n = 6)
8 weeks	15.6 (12.30)	25.2 (6.80)	21.40 (15.45)	30.83 (18.15)	33.50 (13.67)	27.46 (10.61)
12 weeks	22.00 (4.60)	25.0 (7.10)	36.33 (4.41)	38.23 (11.22)	40.76 (7.69)	38.10 (7.48)

SiCaP-23G, silicate -substituted hydroxyapatite granules with 23% strut porosity; SiCaP-23P, silicate-substituted hydroxyapatite Polocramer with 23% strut porosity; SiCaP-32G, silicate-substituted hydroxyapatite granules with 32% strut porosity; SiCaP-32P, silicate-substituted hydroxyapatite Polocramer with 32% strut porosity; SiCaP-46G, silicate-substituted hydroxyapatite granules with 46% strut porosity; SiCaP-46P, silicate-substituted hydroxyapatite Polocramer with 46% strut porosity.

Increasing Strut Porosity in Silicate-substituted Calcium-phosphate Bone Graft Substitutes enhances Osteogenesis Charlie R. Campion, Chaman Chander, Tom Buckland, Karin Hing Journal of Biomedical Materials Research B: Applied Biomaterials- 2011; Vol. 97B, Issue 2: pps: 245-254

MICRO-COMPUTERIZED TOMOGRAPHY RESULTS

8-12 weeks:

- Defects treated with 23% strut porosity bone grafts (Si-CaP-23G and Si-CaP-23P) contained significantly more bone (^{CT}NBV) than that detected in the empty defect (control) sites ($p < 0.05$) **(Figure 6).**
- Evaluation of the absolute graft volume (^{CT}NBV) in Si-CaP-46G and Si-CaP46P treated defects by micro CT indicated that there was a reduction in ^{CT}AGV but these differences were not statistically noteworthy. **(Figure 7)**

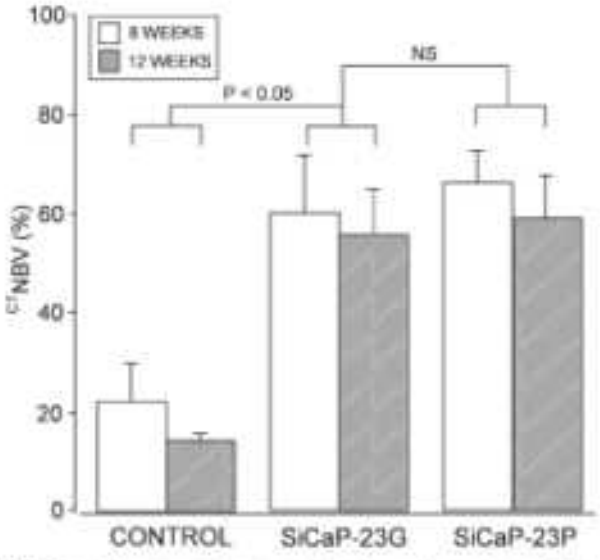


FIGURE 6. Mean percentage normalized bone volume (micro-CT) for SiCaP-23G and SiCaP-23P over 12 weeks.

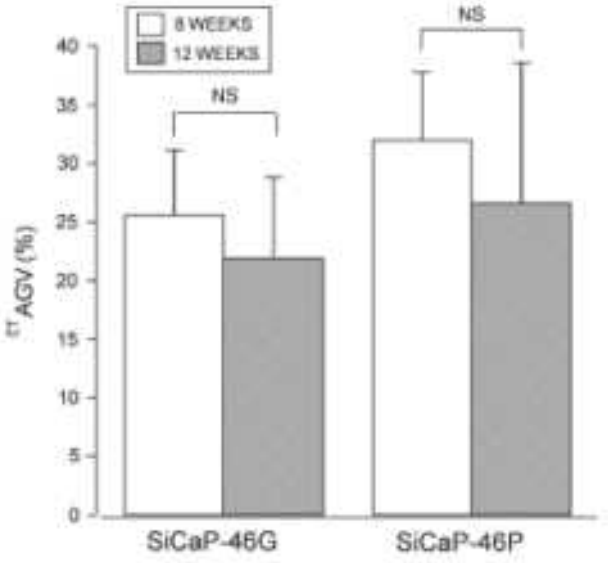


FIGURE 7. Mean percentage absolute graft volume (micro CT) for SiCaP-46G and SiCaP-46P over 12 weeks.

Increasing Strut Porosity in Silicate-substituted Calcium-phosphate Bone Graft Substitutes enhances Osteogenesis Charlie R. Campion, Chaman Chander, Tom Buckland, Karin Hing Journal of Biomedical Materials Research B: Applied Biomaterials- 2011; Vol. 97B, Issue 2: pps: 245-254

CONCLUSION

Results from these studies determined that test material-treated sites had achieved an equilibrium level of bone formation through defect site at 12 weeks, and the volume of bone within the defect had reached a dynamic steady state as modulated by the combination of local host and graft-related environmental and biomechanical factors. Yet the equilibrium level of absolute bone volume was greater in both 23% and 46% strut porosity graft.

Increasing graft matrix strut porosity encouraged earlier neovascularization and increased absolute volume of bone growth without significantly affecting graft stability. Furthermore, evidence of earlier suggested more rapid attainment of an equilibrium bone volume within these microprous grafts. Escalation (both temporal and volumetric) of the healing processes would offer clinical benefits to patients with either conditions or under therapeutic treatments associated with impaired bone repair.

Bone formation in the critically sized defect confirmed relevant osteogenic properties of a porous silicate-substituted (0.8 wt% Si) calcium phosphate bone graft substitute with a strut porosity of 23% when applied as granules or in an aqueous poloxamer carrier.

Efficacy of Silicated Calcium Phosphate Graft in Posterolateral Lumbar Fusion in Sheep
Wheeler DL, Jenis LG, Kovach ME, Marini J, Turner AS Spine J. 2007; 7:308-317

INTRODUCTION

This animal study supports the effectiveness of Si-Cap (ACTIFUSE) compared with autograft in a challenging PLF ovine model. It is important to note that ACTIFUSE granules (2-5 mm) were implanted in a stand-alone fashion with hardware; no local bone, bone marrow aspirate (BMA), or blood was mixed with the ACTIFUSE granules. The various quantifiable measurements used in this study illustrated equivalency of ACTIFUSE to autograft in a preclinical model.*

In addition, the paper highlights the following:

- ACTIFUSE and iliac crest bone graft (ICBG) produced biomechanical and radiographical equivalent fusion masses.
- Both treatments produced an early, normal, woven bone response by 6 months post surgery.
- Bony bridging was equivalent between ACTIFUSE and ICBG.
- Both treatments demonstrate biologically mediated resorption of graft with concurrent bone regeneration.

METHODS

- Groups: ICBG, ACTIFUSE (n=9/group)
- Samples were implanted between L4-L5 transverse process

Computed tomography (CT) was used to assess regenerated bone structure

- Quantitative CT is a calculation combining fusion volume and bone density
- Histological samples were taken at 2 and 6 months to assess healing, bone quality and graft incorporation.
- Histomorphometry (a quantitative measure taken from microscopic images) was used to measure parameters, including the relative fusion area between ACTIFUSE and autograft.
- Biomechanical evaluation between the fused spines and unfused control spines for flexion/extension and lateral bending.

Efficacy of Silicated Calcium Phosphate Graft in Posterolateral Lumbar Fusion in Sheep
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RESULTS

- Fusion mass density and volume were higher for the ACTIFUSE group throughout the healing period
- ACTIFUSE regenerated normal bone tissue morphology, cellularity, and maturation with no inflammatory responses despite that no autograft, bone marrow aspirate, or blood was mixed with the material

- Histomorphometrically, fusion mass was higher for ACTIFUSE and bony bridging was equivalent when compared with autograft treatment
- Both treatment groups achieved 100% bridging fusion after 6 months of healing (Fig 3)

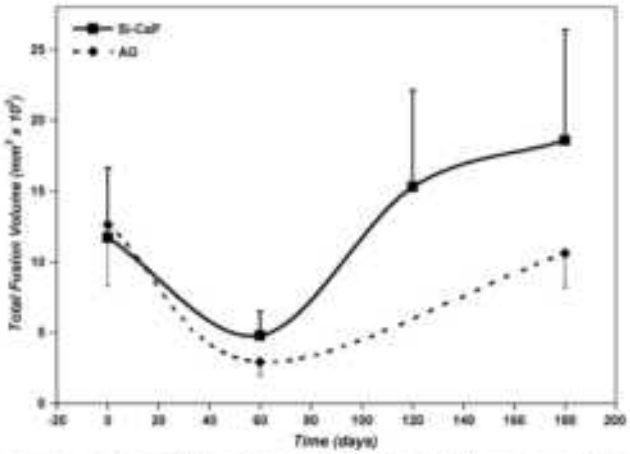

Fig. 3. Total fusion volume over time for the silicated calcium phosphate (Si-CaP) and autograft (AG) treatment groups. No statistical differences were detected between treatment groups ($p < 0.05$, Mean ± SD).

CONCLUSION

ACTIFUSE was biomechanically, radiographically, and histologically comparable to autograft in producing a strong, bony, intertransverse process fusion in an ovine model. It is important to note that both treatment groups achieved 100% bridging fusion after 6 months of healing. Autograft contains important elements required to produce bone (structure, cells, proteins, etc.) but despite this, ACTIFUSE can overcome a significant biological disadvantage and produce an equivalent amount of bone in the same time.

*Preclinical results may not correlate to performance in humans.

Effect of Silicon Level on Rate, Quality, and Progression of Bone Healing within Silicate-substituted Porous Hydroxyapatite Scaffolds.
Hing KA, Revell PA, Smith N, Buckland T. Biomaterials. 2006;27(29):5014-5026

INTRODUCTION

This preclinical study, outlines the benefits of controlled levels of silicate to deliver an optimal biological response, facilitate active bone remodeling, and support a greater volume of bone (both absolute and normalized) ingrowth throughout the study. This study provides the rationale for the 0.8% silicon level.

METHODS

Four grades of silicate-substituted hydroxyapatite materials (Si content 0.2, 0.4, 0.8 and 1.5 wt%) were used.

- Scaffolds were produced with no significant variation in porosity levels
- Bone graft substitute (BGS) samples were implanted into the lower femur of rabbits with surgically (cylindrical) created osseous defects (4.8 ± 0.3 mm diameter, 6-7 mm length).
- The sample size was n=4 per implant retrieval time point.
- Three sections were obtained from each implant, one unstained for fluorescence microscopy, the others stained with toluidine blue or Goldner's trichrome.
- Histomorphometry, using point counting, was used to determine the normalized bone volume percentage.
- Histological evaluation and mineral apposition rate (MAR) were also used to quantify preclinical study results.

RESULTS

- The group containing 0.8 wt% Si supported significantly more bone ingrowth than all other groups at 3 and 6 weeks ($P<0.05$), initially through its elevated mineral apposition rate between weeks 1 and 2, which was significantly higher than that of all other Si-containing groups ($P<0.05$). (Figure 10a)
- The level of silicate substitution also influenced the morphology and stability of the repair, with elevated levels of bone resorption and apposition apparent within other Si-containing groups at time points>3 weeks as compared to the 0 and 0.8 wt% Si groups. (Figure 10b)
- At 12 weeks, the net amount of bone ingrowth continued to rise in the 0, 0.8 and 1.5 wt% groups, apparently as a result of adaptive remodeling throughout the scaffold. Ingrowth levels remained highest in the 0.8 wt% Si group, was characterized by a dense trabecular morphology in the superficial region graduating to a more open network in the deep zone. (Figure 10c)

Effect of Silicon Level on Rate, Quality, and Progression of Bone Healing within Silicate-substituted Porous Hydroxyapatite Scaffolds.
Hing KA, Revell PA, Smith N, Buckland T. Biomaterials. 2006;27(29):5014-5026

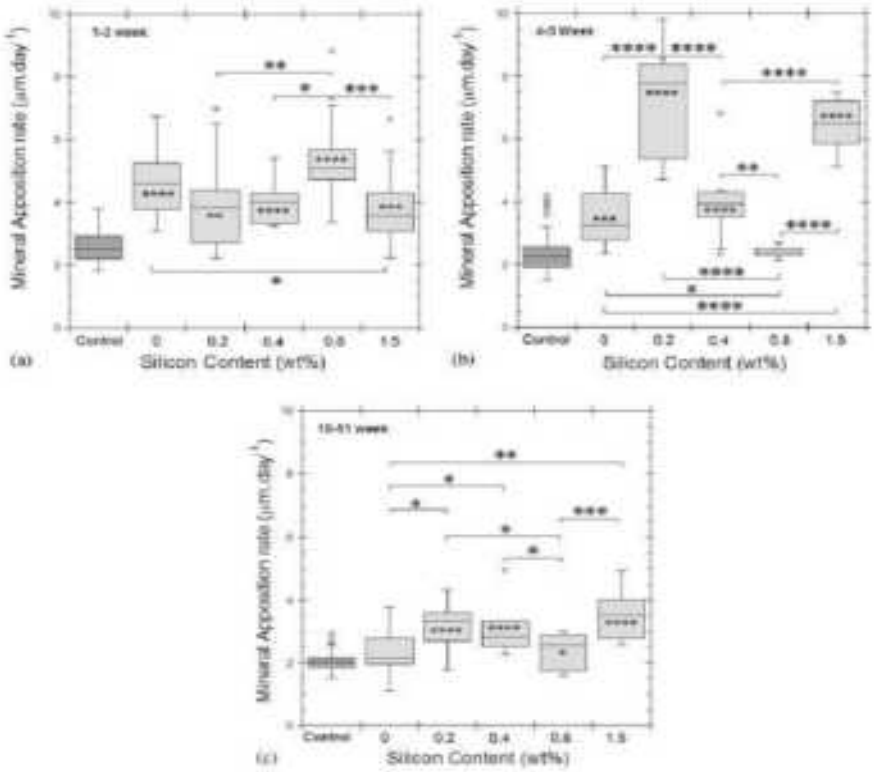

Fig. 10. Variation in the mineral apposition rate of new bone laid down within the various PHA and PSA scaffolds between weeks: (a) 1–2, (b) 4–5 and (c) 10–11 (data: box limits = upper/lower quartiles, error bars = max/min, line = median, outliers = o). [*$P<0.05$, **$P<0.005$, ***$P<0.0005$, ****$P<0.0001$. Small asterisks within the box plots denote level of significance against matched controls].

CONCLUSION

The study outlines the biological responses to various levels of silicate in optimizing bone remodeling and these results highlight the sensitivity of the healing response to Si levels. The study demonstrates the benefits of silicon incorporation on early bone growth. The 0.8 wt% silicon provides the optimal level of silicate, stimulating a strong biological response, rapid bone in-growth and the greatest volume of new bone. The 0.8 wt% silicon provides clear evidence of both bone remodeling and cell-mediated scaffold resorption in an animal model.

Evaluation of an increased strut porosity silicate substituted calcium phosphate, Si-CaP EP, as a synthetic bone graft substitute in spinal fusion surgery: a prospective, open label study Ciaran Bolger; Drew Jones; Steven Czop
European Spine Journal: 2019; Vol. 28: pps: 1733-1742

INTRODUCTION

A prospective, open-label, non-randomized, multicenter clinical study to evaluate efficacy of Si-CaP EP (Inductigraft/Altapore) as bone grafting material in PLF surgery with instrumentation for treatment of spinal disorders.

Silicate-substituted calcium phosphate-enhanced porosity Inductigraft is a synthetic bone graft material with enhanced strut porosity of 31–47% is used in the study.

METHODS

An open-label, phase IV, prospective, multi-Centre clinical study was conducted in 15 research sites across five countries- UK (six centers), Germany, Spain (three each), Hungary (two) and Republic of Ireland (one).

Patients underwent PLF surgery with Inductigraft as the sole graft material, which contains phase-pure, porous Substituted Inductigraft granules [1–2 mm; 80–85% total porosity, 31–47% micro (or strut) porosity and 0.8% Si by weight] in aqueous carrier.

Approximately 20 mL of Inductigraft was placed in the posterolateral gutters between the decorticated transverse processes, which were decorticated to their tips.

RESULTS

Radiographic assessments

- In total, 107 (81.7%) patients completed the study. Most patients had a diagnosis of degenerative disc disease [n=79 (61.2%)] with spinal stenosis, isthmic spondylolisthesis, degenerative spondylolisthesis and 'other' conditions also diagnosed.
- Fusion progression is shown in Table 2 below

Table 2: Spinal fusion success at 6, 12, and 24 months – per protocol population

Visit	Fusion Success	Rate %	95% CI
6 months	59/89	66.3%	55.5–76.0
12 months	88/102	86.3	78.0–92.3
24 months	87/96	90.6	82.9–95.6

Evaluation of an increased strut porosity silicate substituted calcium phosphate, Si-CaP EP, as a synthetic bone graft substitute in spinal fusion surgery: a prospective, open label study Ciaran Bolger; Drew Jones; Steven Czop
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CLINICAL OUTCOMES

I. Pain scores and disability status (Table 3):

- Visual analog scale scores confirmed patients had reduced pain levels for the majority of measured pain domains at month 6 and month 12.
- With the exception of some left leg/buttock pain, back and leg pain was considerably reduced at month 24

Table 3: Oswestry Disability Index (ODI) and Visual Analog Scales (VAS) assessment – per protocol population

Visit	Mean score	Mean change from baseline	95% CI	*P* value
ODI				
Baseline	46.6 (*n* = 99)	–	–	–
6 months	26.2 (*n* = 88)	− 20.6 (*n* = 87)	− 24.5 to − 16.8	< 0.0001
12 months	24.4 (*n* = 100)	− 22.4 (*n* = 97)	− 26.3 to − 18.5	< 0.0001
24 months	33.4 (*n* = 17)	− 19.7 (*n* = 14)	− 34.0 to − 5.4	0.0105
VAS				
Back pain				
Baseline	5.7 (*n* = 99)	–	–	–
6 months	2.5 (*n* = 87)	− 3.3 (*n* = 86)	− 3.9 to − 2.8	< 0.0001
12 months	2.7 (*n* = 98)	− 3.1 (*n* = 95)	− 3.7 to − 2.4	< 0.0001
24 months	4.1 (*n* = 17)	− 3.4 (*n* = 14)	− 5.4 to − 1.5	0.0023
Right leg/buttock pain				
Baseline	4.2 (*n* = 99)	–	–	–
6 months	1.6 (*n* = 87)	− 2.6 (*n* = 86)	− 3.3 to − 1.9	< 0.0001
12 months	1.6 (*n* = 98)	− 2.7 (*n* = 95)	− 3.4 to − 2.0	< 0.0001
24 months	2.5 (*n* = 17)	− 2.2 (*n* = 14)	− 3.8 to − 0.6	0.0106
Left leg/buttock pain				
Baseline	4.2 (*n* = 99)	–	–	–
6 months	1.9 (*n* = 87)	− 2.5 (*n* = 86)	− 3.2 to − 1.7	< 0.0001
12 months	1.5 (*n* = 98)	− 2.7 (*n* = 95)	− 3.4 to − 2.0	< 0.0001
24 months	2.9 (*n* = 17)	− 1.1 (*n* = 14)	− 3.0 to 0.8	0.2178
Total pain				
Baseline	4.73 (*n* = 99)	–	–	–
6 months	2.01 (*n* = 87)	− 2.80 (*n* = 86)	− 3.28 to − 2.33	< 0.0001
12 months	1.92 (*n* = 98)	− 2.84 (*n* = 95)	− 3.32 to − 2.36	< 0.0001
24 months	3.19 (*n* = 17)	− 2.26 (*n* = 14)	− 3.45 to − 1.06	0.0013

The ODI is a self-administered questionnaire measuring back-specific function on a 10-item scale. ODI rates spine-specific disability on a scale of 0 to 100, where 100 is the worst disability

CI confidence interval, *ODI* Oswestry Disability Index, *VAS* visual acuity score; *n* number of patients

a

Evaluation of an increased strut porosity silicate substituted calcium phosphate, Si-CaP EP, as a synthetic bone graft substitute in spinal fusion surgery: a prospective, open label study Ciaran Bolger; Drew Jones; Steven Czop
European Spine Journal: 2019; Vol. 28: pps: 1733-1742

II. Quality of life and neurological status

- The overall success in neurological status (Table 5):
  - At 6 months, patient success in all five parameters were 51.1%
  - At 12 months, patient success was 58.9%
  - At 24 months, patient success was 52.9

Table 5: Neurological Status Success Per Protocol Population

Neurological status	Visit Months	Success[a] N = 102	Rate %	95% CI
Motor	6	79 (n = 88)	89.8	81.5–95.2
	12	91 (n = 98)	92.9	85.8–97.1
	24	16 (n = 17)	94.1	71.3–99.9
Sensory	6	69 (n = 88)	78.4	68.4–86.5
	12	76 (n = 98)	77.6	68.0–85.4
	24	15 (n = 17)	88.2	63.6–98.5
Reflexes	6	70 (n = 88)	79.5	69.6–87.4
	12	78 (n = 97)	80.4	71.1–87.8
	24	11 (n = 17)	64.7	38.3–85.8
Straight leg raise	6	80 (n = 88)	90.9	82.9–96.0
	12	92 (n = 97)	94.8	88.4–98.3
	24	14 (n = 17)	82.4	56.6–96.2
Femoral stretch	6	81 (n = 88)	92.0	84.3–96.7
	12	90 (n = 96)	93.8	86.9–97.7
	24	15 (n = 17)	88.2	63.6–98.5
Overall	6	45 (n = 88)	51.1	40.2–61.9
	12	56 (n = 95)	58.9	48.4–68.9
	24	9 (n = 17)	52.9	27.8–77.0

CLOSURE NOTES

- INDUCTIGRAFT with a strut porosity range of 31–47% (Si-CaP EP) was clinically evaluated in patients undergoing instrumented PLF surgery.
- Enhanced strut porosity INDUCTIGRAFT provided high spinal fusion success rates in PLF surgery that were associated with improved clinical outcomes in patients within 12 months.
- The results of this study support the effective use of INDUCTIGRAFT in instrumented PLF surgery.

A Prospective, Randomized, Multicenter Study Comparing Silicated Calcium Phosphate vs. BMP-2 Synthetic Bone Graft in Posterolateral Instrumented Lumbar Fusion for Degenerative Spinal Disorders Coughlan, Marc; Davies, Mark; Mostert, Adriaan K.; Nanda, Dharmin; Willems, Paul C.; Rosenberg, Geoffrey; Ferch, Richard Spine 2018, Vol.43 (15)-860-868

BACKGROUND

A prospective, randomized, multicenter comparative study in 103 patients with degenerative spinal disorders requiring PLF (1-3 levels), ACTIFUSE Bone Graft Substitute provided fusion rates similar to BMP-2 (Level of Evidence:2)

STUDY OBJECTIVES

Although autologous iliac crest bone has long been considered the gold standard bone graft in PLF, harvesting is associated with significant morbidity at the donor site and prolonged hospitalization. Hence, there is much interest in substitute biomaterials.

ACTIFUSE Bone Graft Substitute is a silicate substituted calcium phosphate synthetic bone graft that combines an optimized osteoconductive scaffold with an aqueous polymer gel resulting in a moldable, cohesive material that facilitates rapid and sustained bone ingrowth. Recombinant human bone morphogenetic protein, in combination with a bovine type I collagen scaffold, or BMP-2 [INFUSE, Medtronic, Inc.], is a bone inductive agent.

Vertebral fusion success rates for ACTIFUSE and BMP-2 were assessed by Coughlan et al1 following PLF using computed tomography (CT) scans evaluated by independent radiographic reviewers at 12 and 24 months. CT scans were graded according to the method of Glassman et al.4 Clinical outcomes included pain scores on a visual analog scale (VAS), Oswestry Disability Index (ODI), SF-36 and adverse events.

RESULTS

A total of 103 patients were enrolled and received treatment (ACTIFUSE, n=51; BMP-2, n=52); 96 patients completed the study. The per protocol (PP) population, defined as all patients who completed the study without protocol deviations, comprised 62 patients with evaluable fusion results (ACTIFUSE, n=35; BMP-2, n=27) at the primary endpoint of 12-month follow-up. Baseline demographics were similar in both treatment groups. Spondylolisthesis (n=49; 47.6%) was the overall diagnosis in the overall population, followed by degenerative disc disease (n=46, 44.7%), stenosis (n=6, 5.8%), and disc herniation (n=2; 1.9%). Table 2

A Prospective, Randomized, Multicenter Study Comparing Silicated Calcium Phosphate vs. BMP-2 Synthetic Bone Graft in Posterolateral Instrumented Lumbar Fusion for Degenerative Spinal Disorders Coughlan, Marc; Davies, Mark; Mostert, Adriaan K.; Nanda, Dharmin; Willems, Paul C.; Rosenberg, Geoffrey; Ferch, Richard Spine 2018, Vol.43 (15)-860-868

TABLE 2. Patients' Baseline Demographic Characteristics

Characteristic	SiCaP (n = 51)	BMP-2 (n = 52)	Total (n = 10
Sex, M/F (%)	27/24 (52.9/47.2)	28/24 (53.8/46.2)	55/48 (53.4/46
Age, yrs	50.8 (11.4)	52.3 (11.6)	51.5 (11.4)
Height, cm	171.9 (11.9)	169.2 (9.3)	170.3 (9.9)
Weight, kg	79.0 (14.5)	81.2 (17.2)	80.2 (15.7)
BMI, kg/m^2	26.9 (4.3)	28.6 (5.0)	27.9 (4.7)
Smoker, N/Y (%)	42/9 (82.4/17.6)	41/11 (78.8/21.2)	83/20 (80.6/19
Diagnosis			
Spondylolisthesis	23 (45.1)	26 (5.8)	49 (47.6)
Degenerative	18 (35.3)	19 (36.5)	37 (35.9)
Isthmic	5 (9.8)	7 (13.5)	12 (11.7)
Degenerative disc disease	25 (49.0)	21 (40.4)	46 (44.7)
Disc herniation	0 (0.0)	2 (3.8)	2 (1.9)

Mean (SD) unless otherwise indicated.
BMP-2 indicates bone morphogenetic protein; SiCaP, silicated calcium phosphate.

CONCLUSIONS

Although BMP-2 has not gained FDA approval for use in PLF, it has been demonstrated as highly efficacious at inducing bone ingrowth in humans. 5-7 In patients undergoing PLF, equivalent bone fusion success was achieved using BMP-2 compared with control patients receiving iliac crest bone graft.8

The study was underpowered due to the number of patients who could not be included in the PP population. This was in part due to the number of protocol deviations, mostly arising from the omission of bulking agent to the BMP-2 material. The quality of life improved for both ACTIFUSE and BMP-2 groups with the level of pain and disability being reduced shown at all postoperative visits.

ACTIFUSE was safe and well tolerated in this study and provided fusion rates similar to those observed in patients receiving BMP-2 bone graft material. On the basis of historical control data, ACTIFUSE may be as useful as iliac crest bone autograft in the context of spine fusion surgery, with less risk of unwanted donor site morbidity.

Lumbar Interbody Fusion Rates with 3D-printed Lamellar Titanium Cages using a Silicate-substituted Calcium Phosphate Bone Graft Michael Mokawem, Galateia Katzouraki, Clare L. Harman, Robert Lee Journal of Clinical Neuroscience, M. Mokawem et al; 2019, Vol. 68, pp 134-139

INTRODUCTION

- Retrospective analysis of a consecutive case series of 93 adult patients with lumbar degenerative disease or deformity requiring interbody cages who underwent TLIF or LLIF surgery with Si-CaP-packed 3D-printed lamellar titanium cages, performed by a single lead surgeon.
- Computed tomography revealed solid fusion in 92/93 (98.9%) patients with good cage integration at the vertebral body interface and no evidence of screw loosening.
- Patient-reported outcomes significantly improved for all parameters 1-year post-operation. Mean VAS significantly declined 1 year following TLIF surgery (back: 5.5; leg: 6.7) and following LLIF surgery (back: 5.9; leg: 6.9). Mean ODI declined 1 year following TLIF surgery (43.0) from crippled to minimal disability and following LLIF surgery (41.2) from severe to minimal disability

MATERIALS & METHODS

- This study was a review of prospectively collected data from a single surgeon based at the Royal National Orthopedic Hospital NHS Trust and Spire Bushey Hospital in the United Kingdom. Data were included from a consecutive case series of 93 eligible adult patients who underwent TLIF or LLIF surgery from 4 November 2015 to 16 October 2017 and provided signed informed consent.
- The primary endpoint was solid fusion 12 months after surgery, assessed using computed tomography.
- Secondary endpoints were patient-reported outcomes; EuroQOL five dimensions (EQ-5D), visual analogue scale (VAS) for pain (EQ-5D VAS), VAS pain scores for leg and back, and Oswestry disability index (ODI).
- The interbody implant used was an off-the-shelf 3D-printed lamellar titanium cage (K2M, Leesburg, VA, USA) packed with Si-CaP bone Inductigraft.

Lumbar Interbody Fusion Rates with 3D-printed Lamellar Titanium Cages using a Silicate-substituted Calcium Phosphate Bone Graft Michael Mokawem, Galateia Katzouraki, Clare L. Harman, Robert Lee Journal of Clinical Neuroscience, M. Mokawem et al; 2019, Vol. 68, pp 134-139

RESULTS

Fusion assessment

- Computed tomography at 12 months demonstrated solid fusion in 92 of 93 (98.9%) patients with good integration of cages at the vertebral body interface and no evidence of screw loosening.
- The single failed fusion occurred in a two-level TLIF for a Grade 2 spondylolisthesis with fusion at L4–L5 and pseudarthrosis at L5–S1. (Figure 2)

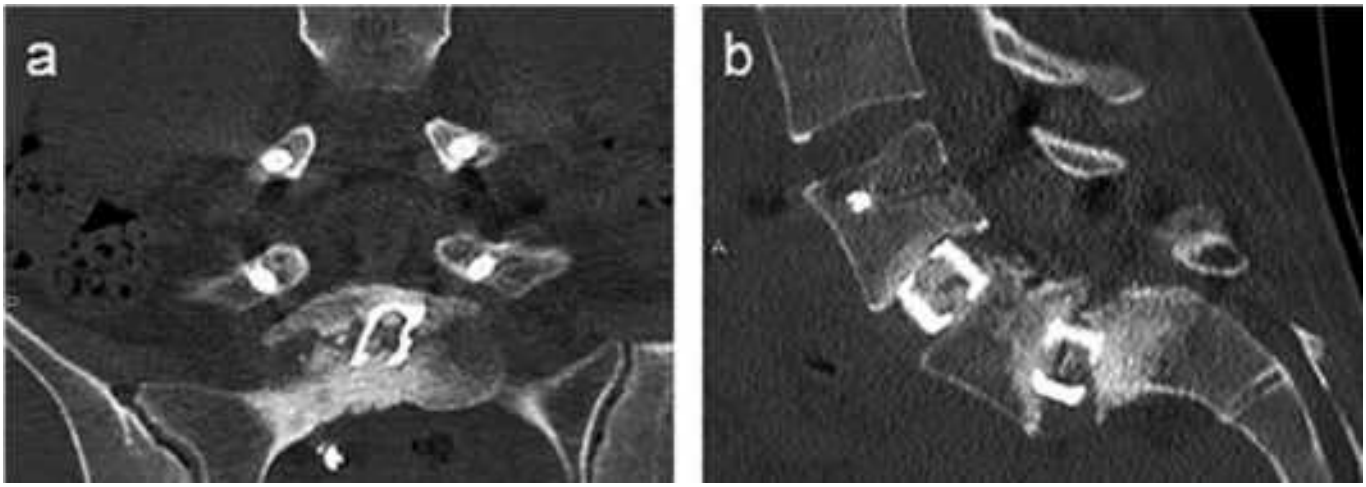

Fig. 2. Computed tomographic scans of the subject with non-union at L5/S1. a) Coronal and b) sagittal computed tomographic scans showing non-union at L5/S1, 1 year after surgery.

Lumbar Interbody Fusion Rates with 3D-printed Lamellar Titanium Cages using a Silicate-substituted Calcium Phosphate Bone Graft Michael Mokawem, Galateia Katzouraki, Clare L. Harman, Robert Lee Journal of Clinical Neuroscience, M. Mokawem et al; 2019, Vol. 68, pp 134-139

Patient-reported outcomes

- Patient-reported outcomes showed clinically significant improvements in all parameters 1-year post-surgery. Pain scores (VAS) in both back and leg decreased following both TLIF and LLIF surgery and quality of life (EQ-5D and EQ-5D VAS) improved in both TLIF and LLIF surgery patients at 6 months and 1 year.(Table 3)
- Mean VAS significantly declined 1- year following TLIF surgery (back: 5.5; leg: 6.7) and following LLIF surgery (back: 5.9; leg: 6.9).
- Mean ODI declined 1 year following TLIF surgery by 43.0 from crippled to minimal disability and following LLIF surgery by 41.2 from severe to minimal disability.

Table 3
Patient-reported outcome scores.

	TLIF (N = 50)	LLIF (N = 43)
EQ-5D		
Pre-Operative	0.29 (0.216)	0.29 (0.191)
Post-Operative (6 months)	0.77 (0.145)	0.78 (0.172)
Post-Operative (1 year)	0.80 (0.153)*	0.80 (0.167)*
Δ-EQ-5D	**0.50 (0.239)**	**0.51 (0.251)**
EQ-5D VAS		
Pre-Operative	43.2 (28.24)	44.3 (24.78)
Post-Operative (6 months)	82.8 (12.24)	82.9 (10.95)
Post-Operative (1 year)	83.0 (12.63)*	87.0 (10.51)*
Δ-EQ-5D VAS	**39.8 (30.25)**	**42.8 (26.24)**
VAS Back		
Pre-Operative	7.4 (3.05)	7.4 (2.33)
Post-Operative (6 months)	2.1 (1.71)	2.0 (1.52)
Post-Operative (1 year)	1.9 (1.46)*	1.5 (1.50)*
Δ-VAS Back	**−5.5 (3.33)**	**−5.9 (2.67)**
VAS Leg		
Pre-Operative	7.9 (2.67)	7.4 (2.72)
Post-Operative (6 months)	1.2 (1.83)	0.7 (1.44)
Post-Operative (1 year)	1.2 (1.57)*	0.5 (1.23)*
Δ-VAS leg	**−6.7 (3.00)**	**−6.9 (3.38)**
ODI (%)		
Pre-Operative	61.1 (21.22)	57.6 (17.23)
Post-Operative (6 months)	22.1 (15.13)	22.5 (13.60)
Post-Operative (1 year)	18.1 (12.92)*	16.5 (15.38)*
Δ-ODI	**−43.0 (21.20)**	**−41.2 (19.50)**

Data were presented as mean (standard deviation). Δ-Outcome indicates change in the outcome 1 year post-operatively. *: $p < 0.001$ compared to the pre-operative values, as defined by paired *t*-test or *z*-test. TLIF = transforaminal lumbar interbody fusion; LLIF = lateral lumbar interbody fusion; EQ-5D = EuroQOL five dimension; VAS = visual analogue scale; ODI = Oswestry Disability Index.

Lumbar Interbody Fusion Rates with 3D-printed Lamellar Titanium Cages using a Silicate-substituted Calcium Phosphate Bone Graft Michael Mokawem, Galateia Katzouraki, Clare L. Harman, Robert Lee Journal of Clinical Neuroscience, M. Mokawem et al; 2019, Vol. 68, pp 134-139

DISCUSSION

- This study is the first prospective evaluation of the spinal fusion rates and safety of Si-CaP-packed 3D-printed lamellar titanium cages in TLIF and LLIF surgery, all completed by a single lead surgeon.
- The study demonstrates that the objectives of deformity correction, indirect or direct decompression, stabilization and fusion can be achieved using Si-CaP-packed 3D-printed lamellar titanium cages in TLIF and LLIF surgery.
- Patient-reported outcomes are supportive of achieving good results, challenging the belief that lumbar spine fusion surgery should not be performed in the adult population with degenerative disease and deformity.

CONCLUSION

Very good fusion rates were demonstrated in adult degenerative disease and deformity with the use of 3-D-printed lamellar titanium cages filled with Si-CaP bone graft.

Outcomes reported by patients confirmed improvements for every result measured, questioning the impression that adult degenerative disease and deformity fails to respond to fusion surgery.

Radiographic and Clinical Outcome of Silicate-substituted Calcium Phosphate (Si-CaP) Ceramic Bone Graft in Spinal Fusion Procedures Marjan Alimi, MD, Rodrigo Navarro-Ramirez, MD, MSc, Karishma Parikh, MD, Innocent Njoku, BS, Christoph P. Hofstetter, MD, Apostolos J. Tsiouris, MD, and Roger Hartl, MD Clinical Spine Surgery: July, 2017; Vol. 30; Issue 6, pps. E845-E852

INTRODUCTION

- Objective of the retrospective cohort study was to evaluate the radiographic and clinical outcome of silicate-substituted calcium phosphate (Si-CaP) utilized as a graft substance in spinal fusion procedures.
- Silicate-substituted calcium phosphate (Si-CaP) constitutes a newer generation of ceramics produced by the addition of calcium and silicate to its phosphate core. This combination provides superior biocompatibility and osteoconductivity as compared with bone substitutes containing solely phosphate.

METHODS

- This was an IRB-approved study. A single surgeon's surgical database was reviewed retrospectively to identify all consecutive patients who underwent various spinal fusion procedures between 2007 and 2011. A total of 234 patients (516 spinal fusion levels) were studied.
- Fusion was evaluated on follow-up CT scans. Clinical outcome was assessed using Oswestry Disability Index, Neck Disability Index, and the visual analogue scale (VAS) for back, leg, neck, and arm pain.

Table 2: Surgical Details

Region and type of surgery	N %
Transforaminal Lumbar Interbody Fusion (TLIF)	57(24.3)
Anterior cervical discectomy and fusion	49 (21)
Extreme lateral interbody fusion	44 (18.8)
Posterior cervical fusion	30 (12.8)
Thoracic	19 (8.1)
AxiaLIF (axial lumbar interbody fusion)	17 (7.3)
Cervical 360 (posterior and anterior cervical)	16 (6.8)
Anterior lumbar interbody fusion	2 (0.9)

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RESULTS

- **Radiologic Evaluation:**
  - The overall fusion rate (14 months) was 82.9% of patients and 86.8% of the levels
  - Among different pathologies, the highest fusion rate was observed in degenerative disease patients (88.3%), followed by trauma patients (86.6%).
  - Patients with metastatic cancer pathology demonstrated the lowest fusion rate (69.2%).
  - The fusion rate for single-level and multi-level procedures were 85.5% and 80.7%, respectively.

The fusion rates for various spinal procedures have been presented separately, in Table 3.

TABLE 3. Fusion Outcome (Evaluated on Average at 14.2 ± 4.3 mo Postoperative)

	%
Anatomic region	
Cervical	92.6
Thoracic	87.0
Lumbar	75.8
Pathology	
Degenerative disease	88.3
Trauma	86.6
Tumor	69.2
Postlaminectomy syndrome	72.7
Surgical procedure	
Transforaminal lumbar interbody fusion	76.3
Anterior cervical discectomy and fusion	94.4
Extreme lateral interbody fusion	82.1
Posterior cervical fusion	84.7
Thoracic	87.0
AxiaLIF (axial lumbar interbody fusion)	71
Cervical 360 (posterior and anterior cervical)	100
Anterior lumbar interbody fusion	100
Single level/multi-level surgery	
Single level	85.5
Multi-level	80.7
Age (y)	
≤65	87.4
> 65	76.7
Smoking status	
Nonsmoker	84.0
Smoker	71.4
Total	82.9
Total excluding AxiaLIF	84.3

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CLINICAL EVALUATION

- The mean duration of clinical follow-up mean was 21.7 ± 0.9 months (range, 8–35 mo.).
- According to the MacNab's criteria, excellent and good outcome was achieved in 87.8% of all patients

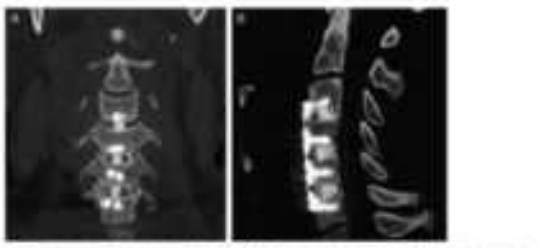
TABLE 4. Clinical Outcomes

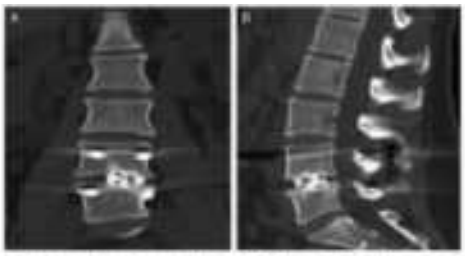
Clinical Outcome	Preoperative	Last Follow-up (21.7 ± 0.49 mo)	*P*
NDI (%)	40.6 ± 2.44	29.3 ± 1.97	0.003*
VAS neck	4.7 ± 0.34	2.7 ± 0.25	0.001*
VAS arm	4.1 ± 0.37	1.7 ± 0.25	< 0.001*
ODI (%)	45.6 ± 1.78	13.3 ± 0.78	0.002*
VAS back	6.1 ± 0.29	3.5 ± 0.29	0.002*
VAS leg	5.6 ± 0.31	2.4 ± 0.26	< 0.001*

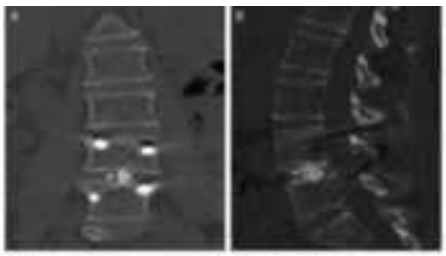
Values are shown as mean ± SE of the mean.
*$P < 0.05$ are considered statistically significant.

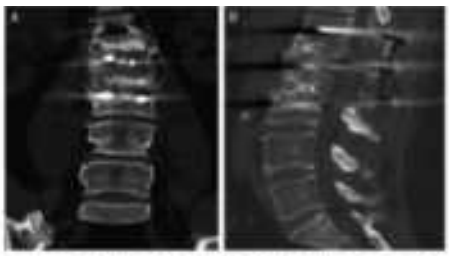
CONCLUSION

- Si-CaP has shown good fusion results, potentially eliminating the need for additional autograft, saving time, and avoiding risks associated with harvesting.
- Si-CaP was used in its manufactured form, convenient for use in both open and MIS surgery, given that it could be applied both directly and/or via a specific MIS delivery system.
- Si-CaP bone graft substitute alone is a viable substitute to autogenous bone for various spinal fusion procedures. After 12 months of follow-up, satisfactory fusion and favorable clinical outcome were observed in majority of patients in the series.
- The overall fusion rate was 84.3% when patients with Axial IF were excluded (Figs. 1–4).









A Prospective, Randomized, Controlled Trial Comparing Radiographic and Clinical Outcomes Between Stand-Alone Laterial Interbody Lumbar Fusion with Either Silicate Calcium Phosphate (ACTIFUSE) or rh_BMP2 (Infuse Bone Graft) Pimenta L, Marchi L, Oliveira L, Coutinho E, Amaral R. A J Neurol Surg A 2013 Nov;74(6):343-50

BACKGROUND

ICBG (iliac crest one graft) has been the benchmark in lumbar spine fusion, however, there are alternatives such as **rh_BMP2** (recombinant human bone morphogenetic protein 2) and **Si-CaP** (silicate calcium phosphate).

This is a study comparing **rh_BMP2** and **Si-CaP** on patients undergoing XLIF (single-level lumbar stand-alone extreme lateral Interbody fusion) to determine improved clinical outcomes and decrease in health costs.

STUDY DESIGN

- 15 patients undertook XLIF using **rh_BMP2**
- 15 patients undertook XLIF using **Si-CaP**
- Results were documented as follows (Table 1):
    - Pain and disability (Oswestry disability index), adverse effects, and neurological issues were assessed at weeks 1 and 6 after surgery as well as months 3, 6, 12, 24 and 36
    - X-rays and CT Scans taken at 6, 12, 24 and 36 months

Table 1 Demographic, clinical, and surgical data

	Groups		*p* value
	SiCaP	rh-BMP2	
Patients	15	15	0.999
Levels	15	15	0.999
Age (years)	49.1 ± 10.7	45.7 ± 11.4	0.237
Gender (female)	73.3%	53.3%	0.256
VAS	71 ± 22	78 ± 17	0.407
ODI	47 ± 13	49 ± 24	0.201
Blood loss (cc)	< 50	< 50	0.999
Surgery duration (min)	70.7 ± 13.3	67.3 ± 8.8	0.186

ODI, Oswestry disability index; VAS, visual analog pain scale; SiCaP, silicate calcium phosphate; rh-BMP2, recombinant human bone morphogenetic protein 2.
Note: Numbers are referred as mean ± standard deviation.

A Prospective, Randomized, Controlled Trial Comparing Radiographic and Clinical Outcomes Between Stand-Alone Laterial Interbody Lumbar Fusion with Either Silicate Calcium Phosphate (ACTIFUSE) or rh_BMP2 (Infuse Bone Graft) Pimenta L, Marchi L, Oliveira L, Coutinho E, Amaral R. A J Neurol Surg A 2013 Nov;74(6):343-50

KEY FINDINGS

No intraoperative complications were observed in either treatment group. Clinical outcomes were similarly improved between bone graft substitutes from baseline to 36 months postoperative

Complication rates between the groups were similar, though with slightly more instances of subsidence in the **Si-CaP** group and higher rates of excessive bone formation and adjacent segment disease in the **rh_BMP2** group.

Fusion rates (Figure 2):

- 6 mo: **Si-CaP** 8%, **rh_BMP2** 33%, p = 0.107
  - 12 mo **Si-CaP** 54%, **rh_BMP2** 67%, p = 0.435
  - 36 mo **Si-CaP** 100%, **rh_BMP2** 100%, p > 0.999

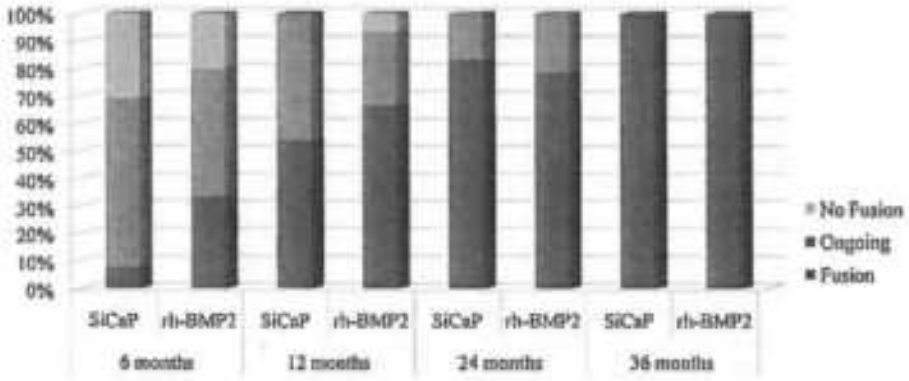


Fig. 2 Fusion status. No statistical difference was found between the two groups. 6-month, $p = 0.170$; 12-month, $p = 0.435$; 24-month, $p = 0.205$; 36-month, $p > 0.999$.

- Rates of fusion at different time points were different between the groups, with the **Si-CaP** patients progressing more slowly toward solid fusion

- **rh_BMP2** seemed to result in more rapid early postoperative fusion, though with one instance of excessive bone formation in one patient that required subsequent surgical intervention

A Prospective, Randomized, Controlled Trial Comparing Radiographic and Clinical Outcomes Between Stand-Alone Laterial Interbody Lumbar Fusion with Either Silicate Calcium Phosphate (ACTIFUSE) or rh_BMP2 (Infuse Bone Graft) Pimenta L, Marchi L, Oliveira L, Coutinho E, Amaral R. A J Neurol Surg A 2013 Nov;74(6):343-50

RESULTS

100% rate of fusion observed in both groups at 36 months with clinical improvements

Complication rates between the control groups that used **rh_BMP2** and **Si-CaP** were fairly similar with fewer occurrences of subsidence in the **rh_BMP2** control group

CONCLUSION

Using **Si-CaP** should be taken under consideration in a stand-alone, single-level XLIF as a viable alternative for cost savings and low graft-related complications.

Silicate-Substituted Calcium Phosphate Ceramic Bone Graft Replacement for Spinal Fusion Procedures Vamsi V. Nagineni , MBBS , Andrew R. James , MBBS, MSc, FRCS , Marjan Alimi , MD , Christoph Hofstetter , MD , PhD, Benjamin J. Shin , BS , Innocent Njoku , Jr, BS, Apostolos John Tsiouris , MD , and Roger Härtl , MD Spine Journal – Lippincott, Williams and Wilkins: 2012, Vol. 37, #20, pp E1264-E1272

INTRODUCTION

- Autogenous bone, commonly obtained from the iliac crest, constitutes the ideal graft and currently represents the "gold standard" for spinal fusion procedures. However, the amount of iliac crest bone available is limited, and its harvesting is associated with increased operative times and with significant donor site morbidity.
- The aim of this study was to evaluate the fusion rate and clinical outcome in spinal fusion procedures using silicate substituted calcium phosphate.

MATERIALS & METHODS

- Retrospective analysis was conducted on all consecutive patients with spinal fusion procedures performed using ACTIFUSE. Cases were excluded when any other bone extenders were used in addition to ACTIFUSE.
- Total 108 patients were enrolled in the study and the indications for surgery were degenerative disease (73%), trauma (16%), metastatic disease (4%), and other (6%). (Table 2)

TABLE 2. Patient Demographics, Overall and by Fusion Outcome

Measure	Value	Fused	Nonfused
Age, mean ± SD (yr)	59.9 ±16.0	56.7 ± 16.3	58.5 ± 14.2
Male:female	51:57	93 (86%)	15 (14%)
Body mass index	28.1	28.3	26.4
Pathology			
Degenerative	79	69 (87%)	10 (13%)
Tumor	5	3 (60%)	2 (40%)
Trauma	17	15 (88%)	2 (12%)
Other	7	6 (86%)	1 (14%)
Smoker			
Yes	12 (11%)	9 (75%)	3 (25%)

Silicate-Substituted Calcium Phosphate Ceramic Bone Graft Replacement for Spinal Fusion Procedures Vamsi V. Nagineni , MBBS , Andrew R. James , MBBS, MSc, FRCS , Marjan Alimi , MD , Christoph Hofstetter , MD , PhD, Benjamin J. Shin , BS , Innocent Njoku , Jr, BS, Apostolos John Tsiouris , MD , and Roger Härtl , MD Spine Journal – Lippincott, Williams and Wilkins: 2012, Vol. 37, #20, pp E1264-E1272

RESULTS

Radiological Evaluation:

- When the follow-up was performed for cervical surgery, 96% of patients (47 of 49) and 97% of levels (103 of 106) fused
- For thoracic procedures, 80% of patients (8 of 10) and 86% of levels (12 of 14) fused
- In lumbar procedures, 77% of patients (38 of 49) and 81% of levels (68 of 84) fused.
- The overall combined fusion rate was 86% of patients (93 of 108) and 90% of levels (183 of 204) (Table 5)
- The clinical outcomes (Table 5) showed a significant improvement in NDI and VAS scores for neck and arm pain with cervical surgery. Lumbar surgery was associated with significant improvement in the ODI, VAS back and leg scores.

CLINICAL EVALUATION

Clinical outcomes at a mean follow-up of 11.8 (+/-5.6) months are detailed in Table 5.

TABLE 5. Comparison Data for Fused and Nonfused Patients

	Fusion	Nonunion	*P*
No. of patients	93	15	
Average age	56.7 ± 16.3	58.4 ± 14.2	0.842
Cervical			
No. of patients	47	2	
Change in NDI	8.3 ± 10.7	25 ± 19.7	0.186
Change in VAS neck	3.7 ± 2.6	4.0 ± 0.7	0.935
Change in VAS arm	4.1 ± 3.2	1.0 ± 1.4	0.103
Thoracic			
No. of patients	8	2	
Change in ODI	12.7 ± 13	4.5 ± 3.5	0.103
Change in VAS back	3.1 ± 5.2	1.0 ± 1.4	0.478
Lumbar			
No. of patients	38	110	
Change in ODI	11 ± 10.1	11.8 ± 14.6	0.820
Change in VAS back	3.4 ± 3.1	2.1 ± 3.1	0.277
Change in VAS leg	4.0 ± 3.4	2.6 ± 3.6	0.248

The values indicate mean ± SD.

NDI indicates Neck Disability Index; VAS, visual analogue scale; ODI, Oswestry Disability Index.

Silicate-Substituted Calcium Phosphate Ceramic Bone Graft Replacement for Spinal Fusion Procedures Vamsi V. Nagineni , MBBS , Andrew R. James , MBBS, MSc, FRCS , Marjan Alimi , MD , Christoph Hofstetter , MD , PhD, Benjamin J. Shin , BS , Innocent Njoku , Jr, BS, Apostolos John Tsiouris , MD , and Roger Härtl , MD Spine Journal – Lippincott, Williams and Wilkins: 2012, Vol. 37, #20, pp E1264-E1272

- Postoperatively, there was a significant improvement after 12 months in Neck Disability Index and VAS scores for neck and arm pain with cervical surgery.
- Lumbar surgery was associated with a significant improvement in the Oswestry Disability Index and VAS back and leg scores.
- There were no statistically significant differences between the clinical outcomes of fused and non-fused patients, except in the Oswestry Disability Index for thoracic surgeries and the VAS arm score for cervical surgeries, both of which contained small numbers

DISCUSSION

- The presence of silicate in the ceramic increases the negative surface charge, and it is hypothesized that this attracts more osteoblasts to the surface of the material.
- Good fusion rates of 90% were demonstrated at a mean 12-month follow-up.
- No revision surgeries for nonunion were required.

COMPLICATIONS

There were five superficial surgical site infections, all successfully treated with antibiotics. Four patients underwent further surgical procedures. There was no loosening of instrumentation due to infection or nonunion in these four patients and no subsequent surgeries required.

- 1 revision laminectomy for a recurrent herniation
- 1 revision laminectomy for a case of post laminectomy syndrome
- 1 patient that required an extension of posterior fixation for pedicle screw failure
- 1 patient for a pedicel screw revision for a misplaced screw

CONCLUSION

ACTIFUSE is a successful bone graft substitute for cervical, thoracic and lumbar spine surgery as well as other surgical approaches, with an overall fusion rate of 90% of levels at a mean follow-up of 12 months. There appeared to be no specific graft-related complications. Use of ACTIFUSE is a viable bone graft substitute as demonstrated by this study.

Bone Incorporation of Silicate-Substituted Calcium Phosphate in 2-State Revision Anterior Crucite Ligament Reconstruction: A Histologic and Radiographic Study Jon von Recum M.D., Johannes Schwaab, M.D, Thorsten Guehring, M.D., Paul-Alfred Grützner, M.D., and Marc Schnetzke, M.D. The Journal of Arthroscopic and Related Surgery, 2017(April); Vol. 33, No. 4: pp-819-827

BACKGROUND

ACL (anterior cruciate ligament) surgeries continue to rise and with it comes graft failures after ACL procedures.
This study was to determine whether Si-CaP (silicate substituted calcium phosphate) could be used as an alternative to autologous bone in the expansion of tunnel defects in a 2-stage revision ACL reconstruction.

STUDY DESIGN (Table 1)

- 40 patients with a mean age of 32; randomized into 2 groups via a 1:1 ratio
- 20 patients in the control group were given autologous iliac crest bone graft for tunnel grafting
- 20 patients received Si-CaP – microgranules (ACTIFUSE MIS System) as a bone graft substitute

Table 1. Measurement of Tunnel Diameter and Analysis of Prior Tunnel Placement Before First-Stage Revision Surgery

	Group 1 (Bone) (n = 20)	Group 2 (Si-CaP) (n = 20)	*P* Value
Tunnel diameter			
Femoral tunnel			
≥10 mm, n	13 (65%)	15 (75%)	.490*
Coronal, mean (SD), mm	11.0 (2.2)	10.0 (1.8)	.092†
Sagittal, mean (SD), mm	10.4 (2.2)	10.7 (2.3)	.723†
Tibial tunnel			
≥10 mm, n	20 (100%)	20 (100%)	>.99*
Coronal, mean (SD), mm	12.1 (1.7)	11.9 (1.4)	.821†
Sagittal, mean (SD), mm	12.3 (2.0)	12.7 (3.0)	.581†
Tunnel placement, n			
Femoral tunnel			
Correct	14 (70%)	12 (60%)	
Incompletely incorrect	6 (30%)	5 (25%)	
Completely incorrect	0	3 (15%)	
Tibial tunnel			
Correct	18 (90%)	18 (90%)	
Incompletely incorrect	2 (10%)	2 (10%)	
Completely incorrect	0	0	

SD, standard deviation; Si-CaP, silicate-substituted calcium phosphate.
*Calculated using χ^2 test.
†Calculated using *t* test.

Bone Incorporation of Silicate-Substituted Calcium Phosphate in 2-State Revision Anterior Crucite Ligament Reconstruction: A Histologic and Radiographic Study Jon von Recum M.D., Johannes Schwaab, M.D, Thorsten Guehring, M.D., Paul-Alfred Grützner, M.D., and Marc Schnetzke, M.D. The Journal of Arthroscopic and Related Surgery, 2017(April); Vol. 33, No. 4: pp-819-827

KEY FINDINGS (Table 4)

- Histologic examination of tunnels (8.7 months after healing) filled with Si-CaP showed that 15% of the area was covered with immature bone formation, 41% with well-organized lamellar bone, and 44% with bone marrow
- In the control group (autologous bone), 58% of the area was covered with well-organized lamellar bone and 42% with the bone marrow
- Quantitative evaluation of the postoperative computer tomography scans showed a trend of better filling rates for the tibial tunnel in patients treated with Si-CaP vs those treated with autologous bone(86% [SD, 17%] vs 78% [SD, 14%]; P=.131
- Intraoperatively, Si-CaP was completely integrated into the original bone tunnel providing good stability for tunnel placement and tendon graft fixation comparable to autologous bone

Table 4. Quantitative Histologic Analysis of Punch Biopsy Specimens

	Lamellar Bone Formation	Immature Bone Formation	Bone Marrow With Si-CaP	Bone Marrow Without Si-CaP
Si-CaP, %				
Femoral tunnel (n = 10)	38 (11)	18 (17)	27 (11)	17 (15)
Tibial tunnel (n = 20)	42 (10)	14 (12)	41 (11)	4 (8)
Both tunnels (n = 30)	41 (10)	15 (14)	32 (12)	12 (14)
Autologous bone (n = 3), %	58 (3)	0	0	42 (3)

NOTE. Data are presented as mean (standard deviation).
Si-CaP, silicate-substituted calcium phosphate.

CONCLUSION

Results of study, six months after the initial tunnel grafting, determined that Si-CaP can provide good stability for revision ACL reconstruction after tunnel grafting comparable to autologous bone.

GLOSSARY

ACTIFUSE (Si-CaP) – An osteostimulative synthetic bone graft substitute2 in which silicate ions selectively replace phosphates to actively accelerate bone formation,*[3] resulting in fusion rates equivalent to iliac crest in both a clinically relevant ovine PLF model4 as well as in a retrospective human study (vs. historical controls)[1]

Angiogenesis – The formation of new blood vessels[1]

Autograft – A tissue that is transplanted from one part to another part of the same body (i.e. iliac crest transplanted into spine)[1]

Autologous Cell Supply – Cells derived from one's own body

Biocompatible – The condition of being compatible with living tissue or a living system by not being toxic or injurious and not causing immunological rejection[1]

Bioresorbable – The materials that can be broken down by the body[2]

BMA – Bone Marrow Aspirate – Bone marrow is the soft tissue inside bones that helps form blood cells. It is found in the hollow part of most bones. Bone marrow aspiration is the removal of a small amount of this tissue in liquid form.[1]

BMP – Bone Morphogenetic Protein – Bone morphogenetic proteins (BMPs) are multi-functional growth factors that belong to the transforming growth factor beta (TGFbeta) superfamily that promote the formation of bone.[3]

Calcium-Phosphates – A class of ceramics containing calcium and phosphate groups that are the chief constituent of bones and teeth (this class includes, HA, B-TCP, etc)$_1$

Cell Mediated Resorption (Of Bone) – Break down of (bony) tissue or material facilitated by cells (osteoclasts)[4]

Collagen – Most abundant protein in the body - Collagen I is the major organic component of bone.[5]

Cortex – The outer or superficial part of an organ or body structure[1]

Cortical Bone – Sometimes called "compact bone" denser bone tissue usually in the cortex (outer edges)[1]

DBM – Demineralized Bone Matrix – Manufactured product derived from decalcified bone (calcium phosphates removed) to expose the organic matrix (collagen and osteoinductive proteins).

ECM - Extra-Cellular Matrix – Matrix produced by cells (collagens, non-collagenous proteins), (in bone: the organic part of the bone tissue)

Fibronectin – A glycoprotein that promotes cellular adhesion and migration[1]

Hematoma – A mass of usually clotted blood that forms in a tissue, organ, or body space as a result of a broken blood vessel[1]

Ionic Substitution – Method of replacing one ionic group for another (i.e. SiO4 for PO4)

INDUCTIGRAFT (Si-CaP 30-Si-CaP EP)
A synthetic bone graft substitute consisting of silicate-substituted calcium phosphate with increased strut porosity. Si-CaP EP has increased strut porosity which mimics the microporous osteocyte lacunae network present in physiological bone.

Lapine Model – Rabbit model. The New Zealand white rabbit is a commonly used model for dorsal and dorsolateral lumbar spine fusion studies.

Microporosity/Strut Porosity – Terms used interchangeably. Used to describe the pore volume fraction of each strut. Strut pores are formed from the interconnected spaces existing between particles of calcium phosphate which have been sintered together to form the struts in the Si-CaP EP scaffold.

Mineralization (of bone) – deposition of calcium phosphate onto the organic (collagenous) matrix[1]

Iliac Crest Autograft (ICBG) – gold standard bone graft material for lumbar spinal surgery despite limitations in the quantity available and complications associated with the harvesting procedure.[2-4]

INFUSE (rhBMP) – recombinant human bone morphogenetic protein

Osseous – of, relating to, or composed of bone[1]

Osteoblast – a bone-forming cell

Osteoclast – any of the large multinucleate cells responsible for bone resorption

Osteoconductive – Material which provide a physical structure into and along which bone may grow[6]

Osteocyte – a cell that is characteristic of adult bone and is isolated in a lacuna of the boney tissue (bone cell)[1]

Osteogenic – Containing the cells required to produce bone[6]

Osteoinductive - Capable of inducing bone formation in a non-bony site by recruiting and inducing (pluripotent) stem cells to become osteoblasts6

Osteostimulative - The ability to signal or activate cells to enhance bone growth[7]

Porosity – the ratio of the volume of interstices (open space) of a material to the volume of its mass (i.e. a material that is 60% porous contains 40% solid material, 60% open space)[1]

Progenitor Cells – a parent cell that gives rise to a distinct cell lineage by a series of cell divisions. Progenitor cells are more differentiated than stem cells and are therefore limited to a specific lineage (will only form a certain tissue)[8]

Proliferate – to grow by rapid reproduction (i.e. cell division)[1]

Resorption – the destruction, disappearance, or dissolution of a tissue or material (can relate to bone or bone graft substitute)[4]

SBGS – Synthetic Bone Graft Substitutes

Scaffolds – a support, either natural or artificial, that maintains tissue contour[2]

Silicate – a salt or ester derived from a silicic acid; especially: any of numerous insoluble often complex metal salts that contain silicon and oxygen in the anion and constitute the largest class of minerals (i.e. SiO2, SiO4)[1]

Standalone - does not need to be mixed with any other components to be effective

Stem Cell - an unspecialized cell that gives rise to differentiated cells (not limited to a specific lineage or forming a specific tissue type)[1]

Substrate – the base on which an organism lives[1]

Trabecular/Cancellous Bone – or spongy bone, light, porous bone enclosing numerous large spaces that give a honeycombed or spongy appearance.[9]

Vitronectin – a glycoprotein of blood plasma that promotes cell adhesion and migration and is similar to fibronectin[1]

Woven Bone - Bony tissue characteristic of the embryonic skeleton in which the collagen fibers of the matrix are arranged irregularly in the form of interlacing networks (developing bone)[2]

Histology – a branch of anatomy that deals with the minute structure of animal and plant tissues as discernible with the microscope.

Histomorphometry – the quantitative study of the microscopic organization and structure of a tissue (as bone) especially by computer-assisted analysis of images formed by a microscope

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PLIF – Posterior Lumbar Interbody Fusion

PLF – Posterolateral Fusion

TLIF - Transforaminal Lumbar Interbody Fusion

LLIF – Lateral Lumbar Interbody Fusion

VAS – Visual Analog Scale

ODI – Oswestry Disability Index

Glossary References:

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Inductigraft

OSTEOINDUCTIVE BONE GRAFT SUBSTITUTE

INDICATIONS FOR USE

- Bone graft substitutes are intended to be used in place of corticocancellous, or cancellous allograft or autograft bone.
- The mechanical environment for such uses experience either low load requirements or compression.

Typical surgical applications for bone graft substitutes are:

- Spinal fusion, where pedicle screw fixation or an interbody cage device is used to relieve the graft site from physiological loads,
- Small void filling, e.g. after removal of a small bone tumour or following bone fracture reduction or in osteotomies, plastic surgery and dental applications.
- It is not intended to be used in place of cortical strut allograft bone where high tensile, torsion and/or bending strength are required. The products are used by surgeons in place of allograft bone (bone from humans stored in bone banks).

RISKS AND WARNINGS

INDUCTIGRAFT should not be used where it could be subject to tension, torsion, compression, shear or bending. A conventional implant (e.g. screw, rod) can protect the graft from such loading actions.

- INDUCTIGRAFT should not be used in volumetrically unconstrained sites (so the graft material cannot move or escape)

Do not overfill or attempt to pressurize the bony defect site, as this may lead to extrusion of the product beyond the site of its intended application and damage to the surrounding tissues, or may lead to fat embolization or embolization of the product into the bloodstream.

- Patient metabolism may compromise bony regeneration

CONTRAINDICATIONS

- Impaction grafting for failed total hip or knee arthroplasty
- Direct load bearing of graft material i.e. In the absence of conventional implants, such as screws and rods
- Infection
- Inability to cover or deliberate non-coverage of graft site using soft tissue
- Avascular or compromised vascular network sites
- Avoid use in patients where in the surgeon's opinion patient lifestyle, compliance and/or physical attributes would compromise clinical outcome
- Medication which could slow bone healing

CE 0086

Actifuse

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